CERTIFICATE OF TRANSLATION

I, Haruko MIWA, am a patent attorney of ION PATENT of Hayakawa-Tonakai Bldg. 3F, 12-5, Iwamoto-cho 2-chome, Chiyoda-ku, Tokyo, Japan, do solemnly and sincerely declare that I am conversant with the Japanese and English languages and I have executed with the best of my ability this translation into English of Japanese Patent Application No. 09-367538 attached hereto which was filed on December 26, 1997 in the name of Hidemitsu NISHIDA et al./MOCHIDA PHARMACEUTICAL CO., LTD. and believe that the translation is true and correct.

Tokyo: June 16, 2003

Haruko Miwa

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[TITLE OF THE INVENTION] AROMATIC COMPOUNDS HAVING CYCLIC AMINO GROUPS AND SALTS THEREOF

[NUMBER OF CLAIMS] 9

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Japanese Patent Application No. 09-367538

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[TYPE OF THE DOCUMENT] Specification

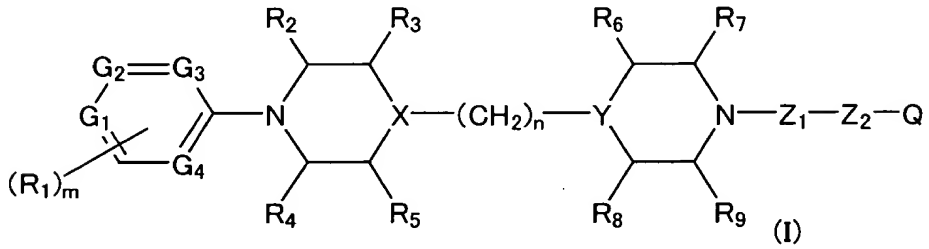
[TITLE OF THE INVENTION] AROMATIC COMPOUNDS HAVING CYCLIC AMINO GROUPS AND SALTS THEREOF

[CLAIM(S)]

[Claim 1]

A compound represented by the following formula (I) or a salt thereof:

[Chemical Formula 1]



(wherein G_1, G_2, G_3 and G_4 are independently CH or N; X and Y are independently CH or N; Z_1 is a group represented by the formulaeO_2- or -CH_2-; Z_2 is a single bond, a lower alkylene group, a lower alkenylene group or a lower alkynylene group; Q is an optionally substituted aryl or an optionally substituted heteroaryl group; R_1 is either any substituent selected from group A (a hydrogen atom, a halogen atom, a trifluoromethyl group, a trifluoromethoxy group, a carboxyl group, a carbamoyl group, an amino group, a cyano group, a nitro group, a lower alkanoyl group, a

lower alkoxyl group, a lower alkoxycarbonyl group, a mono- or di-substituted lower alkylamino group, a lower alkanoylamino group, a cyclic amino group, a phenyl group, a phenoxy group, a benzyloxy group, a benzoyl group, a mercapto group, a lower alkylthio group, a lower alkylthiocarbonyl group, a hydroxyl group or a mono- or di-substituted lower alkylcarbamoyl group), or an oxygen atom that forms a N oxide group with N in any one of G_1 - G_4, or a lower alkyl group, a lower alkoxyl group or a lower alkenyl group those of which may be substituted with a desired number of substituents of group A; R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 each forms a carbonyl group when combined with the carbon atom on the ring to which they are bound, or they are each a hydrogen atom, a carboxyl group, a lower alkoxycarbonyl group, an optionally mono- or di-lower alkyl substituted carbamoyl group, a lower alkoxycarbonylalkylcarbamoyl group, a lower alkoxycarbonylalkyl group, a hydroxy lower alkyl group, a lower alkoxy lower alkyl group, a lower alkyl group, a pyrrolidin-1-ylcarbonyl group, a piperidinocarbonyl group, a morpholinocarbonyl group, a piperazin-1-ylcarbonyl group, a 4-metylpiperazin-1-ylcarbonyl group, an N-phenylcarbamoyl or a group represented by the formula $-CONH(CH_2)_pS(O)_qR_{10}$ or $CONH(CH_2)_rNR_{11}R_{12}$; R_{10}, R_{11} and R_{12} each independently

represents a hydrogen atom, a lower alkyl group, a phenyl group or a lower alkylphenyl group; provided that if any one of the substituents R_2 - R_9 include cyclic group, such cyclic group may be substituted by one or two lower alkyl groups; m and n are independently an integer of 0 - 3, p is an integer of 0 - 4, q is an integer of 0 - 2, and r is an integer of 1 - 4; with the proviso that when X and Y are both N, n is 2 or 3 and Z_1 is $-CH_2-$ those compounds of formula (I) in which R_6 and R_8 in pair or R_7 and R_9 in pair are both carbonyl groups are excluded).

[Claim 2]

The compound or a salt thereof according to claim 1, wherein the optionally substituted aryl or heteroaryl group as said Q is an aryl or heteroaryl group that may be substituted by 1 - 4 groups in any combinations that are selected from among substituents of either group B [a halogen atom, a trifluoromethyl group, a trifluoromethoxy group, a trifluoromethanesulfonyl group, a carboxyl group, a carbamoyl group, an amino group, a cyano group, a nitro group, a lower alkanoyl group, a lower alkoxyl group, a lower alkoxycarbonyl group, a mono- or di-substituted lower alkylamino group, a lower alkanoylamino group, a cyclic amino group, a mercapto group, a lower alkylthio group, a lower alkylthiocarbonyl group, a lower alkylsulfonyl group,

a lower alkylsulfinyl group, a hydroxyl group, a mono- or di-substituted lower alkyl carbamoyl group, an optionally sulfamoyl or carbamoyl substituted amidino group, the formula $-NHCR_{13}-NHR_{14}$ (wherein R_{13} is an optionally cyano-substituted imino group or a group $=CHNO_2$; R_{14} is a hydrogen atom or a methyl group), a phenyl group, a phenoxy group, a heteroaryl group, a heteroaryloxy group, or a group represented by phenyl-S(O)t or heteroaryl-S(O)t (wherein t is an integer of 0 - 2), the heteroaryl group of group B is a 5- or 6-membered aromatic monocyclic group containing not more than four oxygen atoms, sulfur atoms or nitrogen atoms, provided that all aromatic rings of group B may be mono-, di-, or tri-substituted by any substituent of group C (a halogen atom, a trifluoromethyl group, a cyano group, a hydroxyl group, an amino group, a mono- or di-substituted lower alkylamino group, a cyclic amino group, a nitro group, a carboxyl group, a mono- or di-substituted lower alkylcarbamoyl group, a lower alkyl group, a lower alkoxyl group or a lower alkoxycarbonyl group)] or a lower alkyl group that may be substituted by desired number of substituents of group B.

[Claim 3]

The compound or a salt thereof according to claim 1 or 2, wherein at least one of G_1, G_2, G_3 and G_4 is N.

[Claim 4]

The compound or a salt thereof according to claim 3, wherein G_1 is N, m is 0 - 2, n is 1 and Z_1 is $-SO_2-$.

[Claim 5]

The compound or a salt thereof according to claim 1 or 2, wherein each of G_1, G_2, G_3 and G_4 is CH.

[Claim 6]

A pharmaceutical composition containing at least one compound or a salt thereof according to any one of claims 1 - 5 as an active ingredient.

[Claim 7]

The pharmaceutical composition according to claim 6, which is an inhibitor of activated coagulation factor X.

[Claim 8]

The pharmaceutical composition according to claim 6, which is an anticoagulant.

[Claim 9]

The pharmaceutical composition according to claim 6, which is a preventive and/or therapeutic agent for diseases caused by thrombus or embolus.

[DETAILED DESCRIPTION OF THE INVENTION]

[0001]

[Technical Field of the Invention]

This invention relates to orally administrable

aromatic compounds having cyclic amino groups or salts thereof that are useful as pharmaceuticals, particularly as an inhibitor of activated blood coagulation factor X (hereunder referred to as FXa), and which show potent anticoagulation action.

[0002]

[Prior Art]

With the recent shift to western life style and the increasing number of aged people, the incidence of thromboembolic diseases including ischemic heart diseases and many other cardiovascular lesions, in particular, myocardial infarction, cerebral thrombosis, pulmonary embolism and peripheral arteriovenous obstruction is increasing each year and the social importance of treating those diseases is ever increasing. In the treatment and prevention of these thrombotic cases, anticoagulation therapy as well as antiplatelet therapy and fibrinolytic therapy are important medical therapeutic methods. For the treatment and prevention of thrombosis, safety that permits long-term drug administration and the development of a positive and appropriate anticoagulant activity are essential.

[0003]

Heretofore, anticoagulants such as warfarin and

heparin have been used in order to prevent and treat thrombosis due to hypercoagulability but, at the same time, many defects of them have been pointed out, including the risk of bleeding and interactions with other drugs. Warfarin is extensively used in the world as the sole peroral anticoagulant. However, due to its characteristics based on the mechanism of action, the concentration range for the development of efficacy is narrow and yet it takes long to develop efficacy and the half-life in blood is as long as 36 hours; what is more, for several reasons such as the great individual difference of effective dose, it is difficult to control the anticoagulability of warfarin (N. Eng. J. Med. 324 (26) 1865-1875, 1991) and frequent monitoring is necessary to prevent bleeding as a side effect; in addition, warfarin has many other side effects such as nausea, vomiting, diarrhea and alopecia; thus, warfarin is a drug that involves considerable difficulty in clinical use. On the other hand, heparin is extensively used in the world as an intravenously administrable anticoagulant. However, since it is a direct inhibitor of thrombin, heparin has a high risk of bleeding and needs as frequent monitoring as warfarin; what is more, due to its characteristics based on the mechanism of action, adequate coagulation inhibiting effect is not expected at a lowered

antithrombin III level; thus, heparin is a drug that involves considerable difficulty in clinical use. Under these circumstances, the advent of an improved anticoagulant has been desired that has none of the defects inherent in warfarin and heparin.

[0004]

The blood coagulation cascade is a chain reaction involving restricted protein decomposition that starts upon activation of an extringic or intringic coagulation cascade and, once activated, the reaction amplifies like an avalanche. Since the final stage of the blood coagulation cascade is thrombin-mediated conversion of fibrinogen to fibrin, efforts have recently been made to develop thrombin inhibitors; however, drugs that directly inhibit thrombin are known to increase the risk of bleeding. In addition, they have low bioavailability in oral administration and no commercial thrombin inhibitor has ever been proposed that can be administrated perorally.

[0005]

FXa which is located upstream of the coagulation cascade is a key enzyme found at the point of convergence between the extringic and intringic coagulation cascades and one molecule of FXa is known to produce about 100 molecules of thrombin per minute. Hence, an FXa inhibitor

can potentially inhibit the coagulation cascade more efficiently than a thrombin inhibitor (Thrombosis Research, Vol. 19, 339-349, 1980; Mebio, Vol. 14, No. 8, 1997).

[0006]

Compounds that exhibit an FXa inhibiting action have been disclosed in several patents, among which Japanese Patent Application Laid-Opened No. 208946/1993 and WO96/16940 disclose aromatic amidine derivatives, in particular, amidinonaphthyl derivatives, and WO97/38984 discloses cyclic urea compounds having an amidinophenyl group. However, these compounds are still in the process of development and none have been commercialized to date. In addition to low bioavailability, there is a concern about the possible occurrence of side effects such as hypotension and dyspnea due to the amidino group.

[0007]

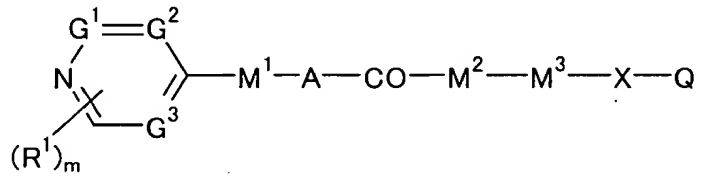
Referring to the compounds it discloses, Japanese Patent Application Laid-Opened No. 208946/1993 teaches using them as an agent for preventing and treating infections with influenza virus by means of their activity in inhibiting the growth of the influenza virus based on the FXa inhibiting action.

Compounds having an aminoheterocyclic group typified by 1-(4-pyridyl)piperidin-4-yl group can be used as an FXa

inhibitor; for example, WO96/10022 discloses

[0008]

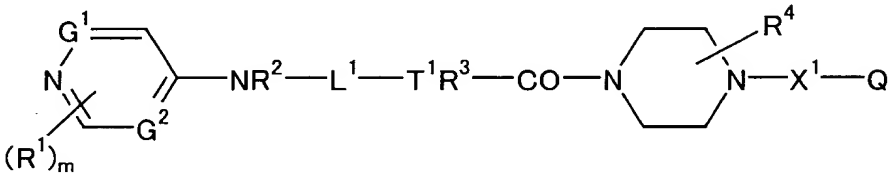
[Chemical Formula 2]



(the definitions of the substituents in the formula are omitted), WO97/29104 discloses

[0009]

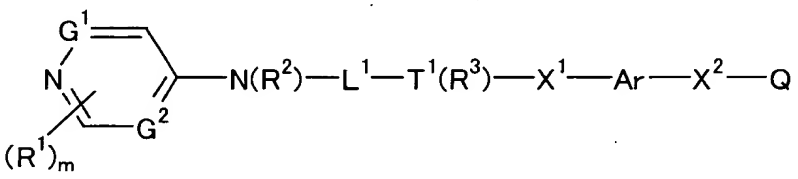
[Chemical Formula 3]



(the definitions of the substituents in the formula are omitted), and WO97/28129 discloses

[0010]

[Chemical Formula 4]



(wherein ... Ar is phenylene or a single 5- or 6-membered aromatic heterocyclic ring containing up to three hetero atoms selected from among a nitrogen atom, an oxygen atom and a sulfur atom, ...).

[0011]

It has been reported that some of the compounds disclosed in those patents have the activity of inhibiting oxidosqualene cyclase (WO97/06802 and WO97/28128). However, as of today, none of these compounds have been commercialized as pharmaceuticals. The five patents mentioned above claim an extremely broad scope of compounds but the bridge group linking two rings comprising combinations of piperazine or piperidine rings requires the presence of a carbonyl group as an essential component and there are no derivatives in which the two rings are bridged by an alkylene group alone or they are directly linked by a single bond.

[0012]

Compounds having an aminoheterocyclic group typified by 1-(4-pyridyl)piperidin-4-yl group can also be used as a platelet agglutination inhibitor and they have been disclosed in many patent applications including, for example, WO94/22834, WO94/22835, WO96/38416, EP718287, WO96/24581 and WO96/19223. However, intending to inhibit GPIIb/IIIa, the compounds disclosed in these patents have a characteristic structure in that an aliphatic carboxyl group, an aliphatic alkoxycarbonyl group or the like is positioned in a terminal side chain of the molecule remote

from the aminoheterocyclic ring. FXa inhibiting action has not been reported for these compounds.

[0013]

While JP-A 63-23874 has disclosed specific compounds in which 2,6- or 3,5-piperazinedione and piperazine are bridged together by a formula $-(CH_2)_n-$ (n is 2 - 4) and have antipsychotic activity, it has not disclosed about blood coagulation.

[0014]

[Problems to be Solved by the Invention]

Under these circumstances, an anticoagulant drug is pressingly needed that has solved at least one of the aforementioned problems by, for example, eliminating interactions with other drugs, reducing side effects such as the risk of bleeding or improving dose response and which is orally administrable, with the particular advantage of being very convenient to use in clinical settings.

[0015]

[Means to Solve the Problems]

With a view to meeting this demand, the present inventors made intensive studies to provide compounds having an enhanced FXa inhibiting action. As a result, they found that among the

aromatic compounds having cyclic amino groups, those in which two rings comprising combinations of piperazine or piperidine rings are bridged together by an alkylene or linked directly by a single bond, particularly those in which the nitrogen atom on either piperazine or piperidine ring is substituted with a group represented by the formula $-Z_1-Z_2-Q$, had an outstanding FXa inhibiting action. The present invention has been accomplished on the basis of this finding.

[0016]

[Embodiment of the Invention]

On the pages that follow, we describe the present invention in detail. The present invention relates to aromatic compounds having cyclic amino groups as represented by the formula (I) to be set forth below or salts thereof.

To be specific, a first aspect of the present invention is to provide compounds represented by the formula (I) or pharmaceutically acceptable salts to be set forth below.

[0017]

A second aspect of the present invention is to provide a pharmaceutical composition characterized by containing a compound represented by the formula (I) or a

pharmaceutically acceptable salt as an active ingredient.

A third aspect of the present invention is to provide an activated blood coagulation factor X (FXa) inhibitor characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt as an active ingredient. More particularly, the inhibitor is a specific FXa inhibitor, or an orally administrable FXa inhibitor, or an orally administrable specific FXa inhibitor.

[0018]

A fourth aspect of the present invention is to provide an anticoagulant characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt as an active ingredient.

A fifth aspect of the present invention is to provide a preventive and/or a therapeutic agent for diseases caused by thrombus or embolus that is characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt as an active ingredient.

A sixth aspect of the present invention is to provide a preventive and/or a therapeutic agent for diseases against which an anticoagulant is effective, characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt as an active ingredient.

[0019]

A seventh aspect of the present invention is to provide a preventive and/or a therapeutic agent for diseases against which an FXa inhibitor is effective, characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt as an active ingredient.

An eighth aspect of the present invention is to provide a preventive and/or therapeutic agent for embolus that accompanies atrial fibrillation, heart valve replacement or valvular heart disease, characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt as an active ingredient. Preferably, it relates to a preventive agent for the onset of cerebral embolism that accompanies atrial fibrillation, heart valve replacement or valvular heart disease.

A ninth aspect of the present invention is to provide a preventive and/or therapeutic agent for transient cerebral ischemic attacks characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt as an active ingredient. It particularly relates to a preventive agent for the recurrence of transient cerebral ischemic attacks.

[0020]

A tenth aspect of the present invention is to provide a preventive and/or therapeutic agent for DIC characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt as an active ingredient.

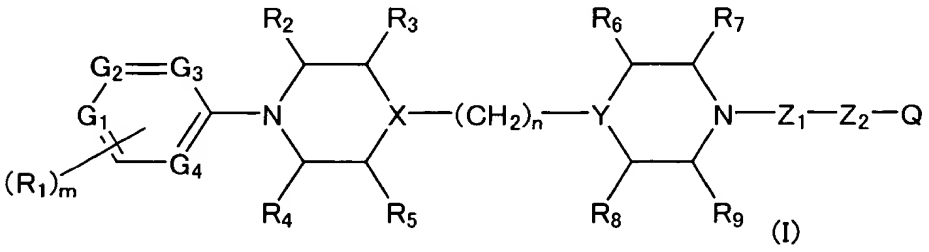
An eleventh aspect of the present invention is to provide a preventive and/or therapeutic agent for influenza viral infections characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt as an active ingredient.

[0021]

The compounds of the present invention are aromatic compounds having cyclic amino groups as represented by the following formula (I) or pharmaceutically acceptable salts thereof:

[0022]

[Chemical Formula 5]



(I)

(wherein the respective symbols have the following meanings

G_1, G_2, G_3 and G_4 are independently CH or N,

X and Y are independently CH or N,

Z_1 is a group represented by the formulaeO_2- or -CH_2-,

Z_2 is a single bond, a lower alkylene group, a lower alkenylene group or a lower alkynylene group,

Q is an optionally substituted aryl or an optionally substituted heteroaryl group,

[0023]

R_1 is either any substituent selected from group A (a hydrogen atom, a halogen atom, a trifluoromethyl group, a trifluoromethoxy group, a carboxyl group, a carbamoyl group, an amino group, a cyano group, a nitro group, a lower alkanoyl group, a lower alkoxyl group, a lower alkoxycarbonyl group, a mono- or di-substituted lower alkylamino group, a lower alkanoylamino group, a cyclic amino group, a phenyl group, a phenoxy group, a benzyloxy group, a benzoyl group, a mercapto group, a lower alkylthio group, a lower alkylthiocarbonyl group, a hydroxyl group or a mono- or di-substituted lower alkylaminocarbonyl group), or an oxygen atom that forms a N oxido group with N in any one of G_1 - G_4, or a lower alkyl group, a lower alkoxyl group or a lower alkenyl group those of which may be substituted with a desired number of substituents of group A;

[0024]

R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 each forms a carbonyl

group when combined with the carbon atom on the ring to which they are bound, or they are each a hydrogen atom, a carboxyl group, a lower alkoxycarbonyl group, an optionally mono- or di-lower alkyl substituted carbamoyl group, a lower alkoxycarbonylalkylcarbamoyl group, a lower alkoxycarbonylalkyl group, a hydroxy lower alkyl group, a lower alkoxy lower alkyl group, a lower alkyl group, a pyrrolidin-1-ylcarbonyl group, a piperidinocarbonyl group, a morpholinocarbonyl group, a piperazin-1-ylcarbonyl group, a 4-metylpiperazin-1-ylcarbonyl group, an N-phenylcarbamoyl or a group represented by the formula $-CONH(CH_2)_pS(O)_qR_{10}$ or $CONH(CH_2)_rNR_{11}R_{12}$; R_{10}, R_{11} and R_{12} each independently represents a hydrogen atom, a lower alkyl group, a phenyl group or a lower alkylphenyl group; provided that if any one of the substituents R_2 - R_9 include cyclic group, such cyclic group may be substituted by one or two lower alkyl groups,

m and n are independently an integer of 0 - 3, p is an integer of 0 - 4, q is an integer of 0 - 2, and r is an integer of 1 - 4.

[0025]

Q is an optionally substituted aryl or an optionally substituted heteroaryl group, and a substituent in Q is a group selected from among substituents of either group B [a

halogen atom, a trifluoromethyl group, a trifluoromethoxy group, a trifluoromethanesulfonyl group, a carboxyl group, a carbamoyl group, an amino group, a cyano group, a nitro group, a lower alkanoyl group, a lower alkoxyl group, a lower alkoxycarbonyl group, a mono- or di-substituted lower alkylamino group, a lower alkanoylamino group, a cyclic amino group, a mercapto group, a lower alkylthio group, a lower alkylthiocarbonyl group, a lower alkylsulfonyl group, a lower alkylsulfinyl group, a hydroxyl group or a mono- or di-substituted lower alkylcarbamoyl group, an optionally sulfamoyl or carbamoyl substituted amidino group, the formula $-NHCR_{13}-NHR_{14}$ (wherein R_{13} is an optionally cyano-substituted imino group or a group $=CHNO_2$; R_{14} is a hydrogen atom or a methyl group), a phenyl group, a phenoxy group, a heteroaryl group, a heteroaryloxy group, or a group represented by phenyl-S(O)t or heteroaryl-S(O)t (wherein t is an integer of 0 - 2), the heteroaryl group of group B is a 5- or 6-membered aromatic monocyclic group containing not more than four oxygen atoms, sulfur atoms or nitrogen atoms, provided that all aromatic rings of group B may be mono-, di- or tri-substituted by any substituent of group C (a halogen atom, a trifluoromethyl group, a cyano group, a hydroxyl group, an amino group, a mono- or di-substituted lower alkylamino group, a cyclic amino group, a nitro group,

a carboxyl group, a mono- or di-substituted lower alkylcarbamoyl group, a lower alkyl group, a lower alkoxyl group or a lower alkoxycarbonyl group)] or a lower alkyl group that may be substituted by a desired number of substituents of group B; an aryl or a heteroaryl in Q may be substituted by 1 - 4 groups in desired combinations of the above-mentioned substituents,

[0026]

with the proviso that when X and Y are both N, n is 2 or 3 and Z_1 is $-CH_2-$ those compounds of formula (I) in which R_6 and R_8 in pair or R_7 and R_9 in pair are both a carbonyl group are excluded from the present invention.

It should also be noted that the compounds of the present invention are clearly different from the compounds described in connection with the prior art in that they have two rings comprising combinations of piperazine or piperidine rings, with no carbonyl group being present in the bridge group between the two rings, and that the molecule has no terminal alkyl side chain that is substituted by a carboxyl group, an alkoxycarbonyl group or the like. In addition, the limitation introduced by the provisio also distinguishes the compounds of the present invention from the compounds of Japanese Patent Application Laid-Opened No. 23874/1988.

[0027]

Further referring to the compounds of the present invention, those in which two piperazine or piperidine rings are bridged by methylene, particularly one that is substituted by a pyridin-4-yl group, have not been synthesized to date since intermediates for them (compounds of the formula (IV) to be set forth below, particularly those of the formula (IV)-b in which G_1 is N and G_2 - G_4 are CH) have been difficult to obtain in a consistent manner. Therefore, although a multitude of compounds were disclosed or contemplated in the aforementioned prior art patents, the compounds of the present invention were not obtained or contemplated as the final compounds. As a result of many considerations on the reaction process and the intensive studies that followed, the present inventors captured the above-mentioned intermediates as reactive ones by the reaction methods to be described below and successfully produced the final compounds in high yield. It should be noted that those intermediates are also applicable to the synthesis of organic compounds other than the final compounds of the present invention.

[0028]

In the definitions of the groups in the structural formulae of the present invention,

the "halogen atom" is exemplified by a fluorine atom, a chlorine atom, a bromine atom and an iodine atom;

the term "lower", unless otherwise noted, refers to a straight or branched carbon chain having 1 - 6 carbon atoms; therefore, the "lower alkyl group" may be exemplified by a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a pentyl group, an isopentyl group, a neopentyl group, a tert-pentyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 1,2-dimethylpropyl group, a hexyl group, an isohexyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 1,1-dimethylbutyl group, a 1,2-dimethylbutyl group, a 2,2-dimethylbutyl group, a 1,3-dimethylbutyl group, a 2,3-dimethylbutyl group, a 3,3-dimethylbutyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 1,1,2-trimethylpropyl group, a 1,2,2-trimethylpropyl group, a 1-ethyl-1-methylpropyl group and a 1-ethyl-2-methylpropyl group; among these, alkyl groups having 1 - 3 carbon atoms are preferred, and a methyl group and an ethyl group are particularly preferred;

[0029]

the "lower alkoxyl group" may be exemplified by a methoxy group, an ethoxy group, a propoxy group, an

isopropoxy group, a butoxy group, an isobutoxy group, a sec-butoxy group, a tert-butoxy group, a pentyloxy(amyloxy) group, an isopentyloxy group, a tert-pentyloxy group, a neopentyloxy group, a 2-methylbutoxy group, a 1,2-dimethylpropoxy group, a 1-ethylpropoxy group and a hexyloxy group; preferred lower alkoxy groups are those having 1 - 3 carbon atoms, and a methoxy group and an ethoxy group are particularly preferred;

[0030]

the "lower alkoxycarbonyl group" may be exemplified by a methoxycarbonyl group, an ethoxycarbonyl group, a propoxycarbonyl group, an isopropoxycarbonyl group, a butoxycarbonyl group, an isobutoxycarbonyl group, a sec-butoxycarbonyl group, a tert-butoxycarbonyl group, a pentyloxycarbonyl group, an isopentyloxycarbonyl group, a neopentyloxycarbonyl group, a tert-pentyloxycarbonyl group, a hexyloxycarbonyl group and other groups that form an ester between a straight-chained or branched alcohol having 1 - 6 carbon atoms and a carboxyl group; preferred lower alkoxycarbonyl groups are those having 1 - 3 carbon atoms, and a methoxycarbonyl group and an ethoxycarbonyl group are given as examples;

[0031]

the "mono- or di-substituted lower alkylamino group"

is meant an amino group in which one or two hydrogen atoms are replaced by the above-defined "lower alkyl group"; specific examples include a methylamino group, an ethylamino group, a propylamino group, an isopropylamino group, a butylamino group, an isobutylamino group, a pentylamino group, an isopentylamino group, a hexylamino group and an isohexylamino group. The dialkylamino group may be of a symmetric type which is di-substituted by a straight-chained or branched alkyl group having 1 - 6 carbon atoms, as exemplified by a dimethylamino group, a diethylamino group, a dipropylamino group, a diisopropylamino group, a dibutylamino group and a dipentylamino group, or it may be of a type that is asymmetrically substituted by a straight-chained or branched alkyl group having 1 - 6 carbon atoms, as exemplified by an ethylmethylamino group, a methylpropylamino group, an ethylpropylamino group, a butylmethylamino group, a butylethylamino group and a butylpropylamino group;

[0032]

the "cyclic amino group" may be a cyclic cycloalklylamino group that may have a branched chain of 2 - 6 carbon atoms, as exemplified by a pyrrolidinyl group, a piperidinyl group or a methylpiperidinyl group, or it may

be a saturated cyclic amino group as exemplified by a morpholino group or a piperazinyl group;

[0033]

the "lower alkylene group" is an alkylene group having 1 - 6 carbon atoms, as exemplified by a methylene group, an ethylene group, a methylmethylene group, a trimethylene group, a dimethylmethylene group, a tetramethylene group, a methyltrimethylene group, an ethylethylene group, a dimethylethylene group, an ethylmethylmethylene group, a pentamethylene group, a methyltetramethylene group, a dimethyltrimethylene group, a trimethylethylene group, a dimethylmethylene group, a hexamethylene group, a methylpentamethylene group and a dimethyltetramethylene group; preferred are alkylene groups having 1 - 3 carbon atoms as exemplified by a methylene group, an ethylene group, a methylmethylene group, a trimethylene group and a dimethylmethylene group, with a methylene group and an ethylene group being more preferred;

[0034]

the "lower alkenylene group" is an alkenylene group having 1 - 6 carbon atoms, as exemplified by a vinylene group, a propenylene group, an isopropenylene group, a 2-butenylene group and a 1,3-butadienylene group, and a vinylene group is preferred;

the "lower alkynylene group" may be exemplified by an ethynylene group and a propynylene group;

[0035]

the "lower alkanoyl group" may be exemplified by a formyl group, an acetyl group, a propionyl group, a butyryl group, an isobutyryl group, a valeryl group, an isovaleryl group, a pivaloyl group and a hexanoyl group, and an acetyl group, a propionyl group and a butyryl group are preferred;

[0036]

the "lower alkanoylamino group" is a group in which the hydrogen atom in an amino group is substituted by the above-defined lower alkanoyl group and examples include a formylamino group, an acetylamino group, a propionylamino group, a butyrylamino group, an isobutyrylamino group, a valerylamino group, an isovalerylamino group, a pivaloylamino group and a hexanoylamino group, with an acetyl group, an amino group, a propionylamino group and a butyrylamino group being preferred;

[0037]

the "lower alkylthio group" may be a group in which the hydrogen atom in a mercapto group is substituted by the above-defined "lower alkyl group" and examples include a methylthio group, an ethylthio group, a propylthio group, an isopropylthio group, a butylthio group, an isobutylthio

group, a pentylthio group and a hexylthio group;

[0038]

the "aryl group", unless otherwise noted, is an aryl group in the form of a monocyclic or fused hydrocarbon ring having 6 - 14 carbon atoms and may specifically be exemplified by a phenyl group, a naphthyl group, a biphenyl group and an anthryl group, with a phenyl group, a naphthyl group and a biphenyl group being preferred;

[0039]

the "heteroaryl group", unless otherwise noted, may be a monocyclic or fused cyclic heteroaryl group having 1 - 4 hetero atoms comprising oxygen, sulfur or nitrogen atoms, as exemplified by a furyl group, a thienyl group, a pyrrolyl group, a pyrazolyl group, an imidazolyl group, an isothiazolyl group, an oxazolyl group, an isoxazolyl group, a thiazolyl group, a pyridyl group, a pyridazinyl group, a pyrimidinyl group, a pyrazinyl group, a triazinyl group, a benzimidazolyl group, a benzofuranyl group, a 1,2-benzoisoxazolyl group, a benzoxazolyl group, a benzothiazolyl group, an indolyl group, an imidazopyridyl group, an oxazolopyridyl group, an isothiazolopyridyl group, a benzothienyl group, a naphthyridinyl group, a quinolyl group, an isoquinolyl group, a quinazolinyl group, a quinolizinyl group, a quinoxalinyl group, a cinnolinyl

group, a benzoxazinyl group, a benzothiazinyl group, a 1,2,3-triazolyl group, a 1,2,4-triazolyl group, an oxadiazolyl group, a furazanyl group, a thiadiazolyl group, a tetrazolyl group, a dibenzofuranyl group, a dibenzothienyl group, a 1,2,3,4-tetrahydroquinolyl group and a 1,2,3,4-tetrahydroisoquinolyl group;

[0040]

the "lower alkylthiocarbonyl group" is the same as the above-defined "lower alkanoyl group" except that the carbonyl group is replaced by a thiocarbonyl group and examples include a methylthiocarbonyl group, an ethylthiocarbonyl group and a propylthiocarbonyl group;

[0041]

the "optionally mono- or di-lower alkyl substituted carbamoyl group" may be exemplified by a carbamoyl group, an N-methylcarbamoyl group, an N-ethylcarbamoyl group, an N,N-dimethylcarbamoyl group, an N,N-diethylcarbamoyl group and an N-ethyl-N-methylcarbamoyl group;

[0042]

the "lower alkoxycarbonylalkylcarbamoyl group" is meant a mono- or di-lower alkyl substituted carbamoyl group in which alkyl group is substituted by the above-defined "lower alkoxycarbonyl group" and examples include a methoxycarbonylmethylcarbamoyl group,

ethoxycarbonylmethylcarbamoyl group and an ethoxycarbonylethylcarbamoyl group;

[0043]

the "lower alkoxycarbonylalkyl group" is meant a lower alkyl group substituted by the above-defined "lower alkoxycarbonyl group" and examples include a methoxycarbonylmethyl group and an ethoxycarbonylethyl group;

[0044]

the "hydroxy lower alkyl group" is meant a lower alkyl group in which one or two hydrogen atoms are replaced by the hydroxyl group and examples include a hydroxymethyl group, a 2-hydroxyethyl group, a 2-hydroxypropyl group and a 2,3-dihydroxypropyl group;

[0045]

the "lower alkoxy lower alkyl group" is meant a "lower alkyl group" substituted by the above-defined "lower alkoxyl group"; namely examples include a methoxymethyl group and a 2-ethoxyethyl group; it includes the group which is further substituted by a "lower alkoxyl group" and examples include a 2-methoxy-ethoxymethyl group;

[0046]

the "lower alkylsulfonyl group" is the same as the above-defined "lower alkylthio group" except that the

sulfur atom is replaced by a sulfonyl group and examples include a methanesulfonyl group, an ethanesulfonyl group and a propanesulfonyl group;

[0047]

the "lower alkylsulfinyl group" is the same as the above-defined "lower alkylthio group" except that the sulfur atom is replaced by a sulfinyl group and examples include a methanesulfinyl group, an ethanesulfinyl group and a propanesulfinyl group;

[0048]

the "heteroaryloxy group" is a hydroxyl group having the hydrogen atom replaced by the above-defined "heteroaryl group".

[0049]

The following are the preferred definitions of the substituents in the compounds of the present invention.

As for G_1 - G_4 in the formula (I), it is preferred that at least one of G_1, G_2, G_3 and G_4 is N; more preferred cases are as follows: G_1 is N and G_2, G_3 and G_4 are CH; G_2 is N and G_1, G_3 and G_4 are CH; G_3 is N and G_1, G_2 and G_4 are CH; G_1 and G_2 are N and G_3 and G_4 are CH; G_1 and G_3 are N and G_2 and G_4 are CH; G_1, G_2 and G_4 are N and G_3 is CH; and G_1, G_3 and G_4 are N and G_2 is CH; further preferred cases are as follows: G_1 is N and G_2, G_3 and G_4 are CH; G_1 and G_3 are N and G_2 and

G_4 are CH; G_1, G_3 and G_4 are N and G_2 is CH. While N in any one of G_1 - G_4 mentioned above may combine with R_1 to form N-oxide, it is preferred for G_1 to make N-oxide.

[0050]

Preferably, R_1 is a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, an amino group, a methyl group, an ethyl group, a methoxy group, a trifluoromethyl group, a trifluoromethoxy group, a cyano group, an aminomethyl group, a hydroxyl group, a hydroxymethyl group, a carbamoyl group, or an N-oxide group formed in combination with any one of G_1 - G_4.

Preferably, m is 0, 1, 2 or 3, and more preferably 0, 1 or 2.

[0051]

It is preferred that R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 each forms a carbonyl group when combined with the carbon atom on the ring to which they are bound, or they are each a hydrogen atom, a carboxyl group, a lower alkoxycarbonyl group, an optionally mono- or di-lower alkyl substituted carbamoyl group, a lower alkoxycarbonylalkylcarbamoyl group, a lower alkoxycarbonylalkyl group, a hydroxy lower alkyl group, a lower alkoxy lower alkyl group, a lower alkyl group, a pyrrolidin-1-ylcarbonyl group, a piperidinocarbonyl group, a morpholinocarbonyl group, a

piperazin-1-ylcarbonyl group, a 4-metylpiperazin-1-ylcarbonyl group, an N-phenylcarbamoyl or a benzyl group; also provided that if any one of the substituents R_2 - R_9 is cyclic, such cyclic group may be substituted by one or two lower alkyl groups;

provided that if any one of the substituents R_2 - R_9 include cyclic group, such cyclic group may be substituted by one or two lower alkyl groups;

more preferably, R_2, R_3, R_4 and R_5 each independently represents a hydrogen atom, a methyl group or an ethyl group whereas R_6, R_7, R_8 and R_9 each forms a carbonyl group when combined with the carbon atom on the ring to which they are bound, or they are each a hydrogen atom, a carboxyl group, a methoxycarbonyl group, an ethoxycarbonyl group, a carbamoyl group, an N-methylcarbamoyl group, N,N-dimethylcarbamoyl group, a carboxymethyl group, a methoxycarbonylmethyl group, an ethoxycarbonylmethyl group, an hydroxymethyl group, a methoxymethyl group, a methyl group, an ethyl group, a pyrrolidin-1-ylcarbonyl group, a piperidinocarbonyl group, a morpholinocarbonyl group, a piperazin-1-ylcarbonyl group, a 4-metylpiperazin-1-ylcarbonyl group, an N-phenylcarbamoyl or a group represented by the formula $-CONH(CH_2)_pS(O)_qR_{10}$ or the formula $-CONH(CH_2)_rNR_{11}R_{12}$; it is preferred that R_{10}, R_{11} and R_{12} each

independently represents a hydrogen atom, a methyl group, an ethyl group, a phenyl group or a benzyl group, p is an integer of 0, 1 or 2, q is 0, 1 or 2, and r is 1 or 2;

provided that if any one of the substituents R_6 - R_9 include cyclic group, such cyclic group may be substituted by one or two methyl groups or ethyl groups;

more preferably, R_2, R_3, R_4 and R_5 each independently represents a hydrogen atom whereas R_6, R_7, R_8 and R_9 form a carbonyl group when combined with the carbon atom on the ring to which they are bound, or they each represent a hydrogen atom, a carboxyl group, a methoxycarbonyl group, an ethoxycarbonyl group, a carbamoyl group, an N-methylcarbamoyl group, a carboxymethyl group, a methoxycarbonylmethyl group, an hydroxymethyl group, a methyl group, an ethyl group, piperidinocarbonyl group or a benzyl group;

[0052]

X and Y each independently represents CH or N; the preferred cases are where X is CH and Y is CH or N and where X is N and Y is CH; the more preferred case is where X is CH and Y is N;

n is preferably 0, 1, 2 or 3, more preferably 0 or 1;

[0053]

Z1 is preferably the formulaeO_2- or -CH_2-, more

preferably $-SO_2-$;

Z_2 is preferably a single bond, a lower alkylene group or a lower alkenylene group;

the aryl group Q is an aryl group in the form of a monocylic or fused hydrocarbon ring having 6 - 14 carbon atoms and is preferably a phenyl group, a biphenyl group, a 1-naphthyl group or a 2-naphthyl group; the heteroaryl group is a monocyclic or fused cyclic heteroaryl group having 1 - 4 hetero atoms comprising oxygen, sulfur or nitrogen atoms and is preferably a thienyl group, a benzofuranyl group, a benzothienyl group, a benzothiazolyl group, a quinolyl group, a isoquinolyl group, a 1,2,3,4-tetrahydroquinolyl group, a 1,2,3,4-tetrahydroisoquinolyl group, a pyridylphenyl group or a pyridylthienyl group; these groups may preferably be substituted by any one of the above-listed substituents of group B;

[0054]

the group represented by the formula $-Z_2-Q-$ is preferably a phenyl group, a 1-naphthyl group, a 2-naphthyl group, a biphenylyl group, a benzyl group, a phenethyl group, a styryl group, a 2-phenylethynyl group, a benzofuranyl group, a benzothienyl group, a benzothiazolyl group, a quinolyl group, a isoquinolyl group, a 1,2,3,4-tetrahydroquinolyl group, a 1,2,3,4-tetrahydroisoquinolyl

group;

these groups are either unsubstituted or preferably mono-, di- or tri-substituted by any substituent selected from among a hydroxyl group, an amino group, an amidino group, a sulfamoylamidino group, an N'-cyano-guanidino group, an N'-methyl-2-nitro-1,1-ethenediamino group, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, a cyano group, a trifluoromethyl group, a nitro group, a carboxyl group, a carbamoyl group, a methoxycarbonyl group, an ethoxycarbonyl group, a methyl group, an ethyl group, a methoxy group and an ethoxy group.

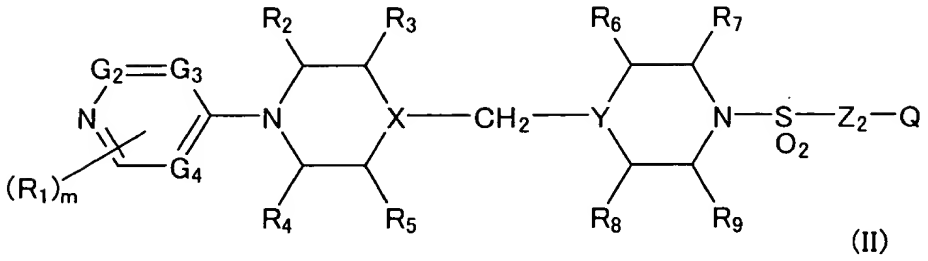
[0055]

The compounds of the present invention are those of the formula (I) or salts thereof. The following are specific examples of the compounds having the preferred combinations of substituents.

(1) Compounds of the formula (I) where at least one of G_1, G_2, G_3 and G_4 is N or salts thereof are preferred.

More preferred are the compounds where at least G_1 is N, m is 0 - 2, n is 1 and Z_1 is $-SO_2-$ or salts thereof. In this case, the formula (I) may be rewritten as the following formula (II), wherein the other respective substituents have the same meanings as in the formula (I):

[Chemical Formula 6]



(II)

[0056]

Further preferred are the following compounds or salts thereof: in the combination of G_2 - G_4, G_2, G_3 and G_4 are CH, or G_3 is N and G_2 and G_4 are CH, or G_3 and G_4 are N and G_2 is CH; R_1 is a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, an amino group, a methyl group, an ethyl group, a methoxy group, a trifluoromethyl group, a trifluoromethoxy group, a cyano group, an aminomethyl group, a hydroxyl group, a hydroxymethyl group, a carbamoyl group, or an N-oxide group formed together with any one of G_1 - G_4; R_2, R_3, R_4 and R_5 each independently represents a hydrogen atom, a methyl group or an ethyl group; R_6, R_7, R_8 and R_9 each forms a carbonyl group when combined with the carbon atom on the ring to which they are bound, or they are each a hydrogen atom, a carboxyl group, a methoxycarbonyl group, an ethoxycarbonyl group, a carbamoyl group, an N-methylcarbamoyl group, an N,N-dimethylcarbamoyl group, a carboxymethyl group, a methoxycarbonylmethyl group, an ethoxycarbonylmethyl group, a hydroxymethyl group, a methoxymethyl group, a methyl

group, an ethyl group, a pyrrolidin-1-ylcarbonyl group, a piperidinocarbonyl group, a morpholinocarbonyl group, a piperazin-1-ylcarbonyl group, a 4-methylpiperazin-1-ylcarbonyl group or a benzyl group (if any one of the substituents R_6 - R_9 is cyclic, such cyclic group may be substituted by one or two methyl or ethyl groups);

X is CH and Y is CH or N, or X is N and Y is CH;

Z_2 is a single bond, a lower alkylene group or a lower alkenylene group;

Q is a phenyl group, a biphenylyl group, a 1-naphthyl group or 2-naphthyl group, a thienyl group, a benzofuranyl group, a benzothienyl group, a benzothiazolyl group, a quinolyl group, a isoquinolyl group, a 1,2,3,4-tetrahydroquinolyl group, a 1,2,3,4-tetrahydroisoquinolyl group, a pyridylphenyl group or a pyridylthienyl group, provided that these groups may be mono, di- or tri-substituted by a substituent of the above-defined group B or by a lower alkyl group which may be mono-, di- or tri-substituted by a substituent of group B.

[0057]

Particularly preferred are the following compounds or salts thereof: G_1 is N, G_2, G_3 and G_4 are CH; R_1 is a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, an amino group, a methyl group, an

ethyl group, a methoxy group, a trifluoromethyl group, a trifluoromethoxy group, a cyano group, an aminomethyl group, a hydroxyl group, a hydroxymethyl group, a carbamoyl group, or an N-oxide group formed together with G_1; m is 0, 1 or 2; R_2, R_3, R_4 and R_5 are each a hydrogen atom; R_6, R_7, R_8 and R_9 each forms a carbonyl group when combined with the carbon atom on the ring to which they are bound, or they are each a hydrogen atom, a carboxyl group, a methoxycarbonyl group, an ethoxycarbonyl group, a carbamoyl group, an N-methylcarbamoyl group, a carboxymethyl group, a methoxycarbonylmethyl group, an N-(2-ethylthioethyl)carbamoyl group, a hydroxymethyl group, a methyl group, an ethyl group, a piperidinocarbonyl group or a benzyl group; X is CH and Y is N; the group represented by the formula $-Z_2-Q$ is a phenyl group, a 1-naphthyl group, a 2-naphthyl group, a biphenylyl group, a benzyl group, a phenethyl group, a styryl group, a 2-phenylethynyl group, a benzofuranyl group, a benzothienyl group, a benzothiazolyl group, a dibenzofuranyl group, a quinolyl group, a isoquinolyl group, a 1,2,3,4-tetrahydroquinolyl group or a 1,2,3,4-tetrahydroisoquinolyl group; these aromatic rings are either unsubstituted or mono-, di- or tri-substituted by any substituent selected from among a hydroxyl group, an amino group, a fluorine atom, a chlorine atom, a bromine

atom, an iodine atom, a cyano group, a trifluoromethyl group, a nitro group, a carboxyl group, a carbamoyl group, a methoxycarbonyl group, an ethoxycarbonyl group, a methyl group, an ethyl group, a methoxy group, an ethoxy group, an amidino group, a sulfamoylamidino group, an N'-cyano-guanidino group and an N'-methyl-2-nitro-1,1-ethenediamino group.

[0058]

(2) Compounds of the formula (I) wherein each of G_1, G_2, G_3 and G_4 is CH or salts thereof are preferred.

More preferred are the following compounds or salts thereof: R_1 is a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, an amino group, a methyl group, an ethyl group, a methoxy group, a trifluoromethyl group, a trifluoromethoxy group, a cyano group, an aminomethyl group, a hydroxyl group, a hydroxymethyl group, or a carbamoyl group; m is 0, 1 or 2; R_2, R_3, R_4 and R_5 are each a hydrogen atom; R_6, R_7, R_8 and R_9 each forms a carbonyl group when combined with the carbon atom on the ring to which they are bound, or they are each a hydrogen atom, a carboxyl group, a methoxycarbonyl group, an ethoxycarbonyl group, a carbamoyl group, an N-methylcarbamoyl group, a carboxymethyl group, a methoxycarbonylmethyl group, an N-(2-

ethylthioethyl)carbamoyl group, a hydroxymethyl group, a methyl group, an ethyl group, a piperidinocarbonyl group or a benzyl group; X is CH and Y is N; the group represented by the formula $-Z_2-Q$ is a phenyl group, a 1-naphthyl group, a 2-naphthyl group, a biphenylyl group, a benzyl group, a phenethyl group, a styryl group, a 2-phenylethynyl group, a benzofuranyl group, a benzothienyl group, a benzothiazolyl group, a dibenzofuranyl group, a 1,2,3,4-tetrahydroquinolyl group or a 1,2,3,4-tetrahydroisoquinolyl group; these aromatic rings are either unsubstituted or mono-, di- or tri-substituted by any substituent selected from among a hydroxyl group, an amino group, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, a cyano group, a trifluoromethyl group, a nitro group, a carboxyl group, a carbamoyl group, a methoxycarbonyl group, an ethoxycarbonyl group, a methyl group, an ethyl group, a methoxy group, an ethoxy group, an amidino group, a sulfamoylamidino group, an N'-cyano-guanidino group and an N'-methyl-2-nitro-1,1-ethenediamino group.

[0059]

The compounds of the present invention sometimes have asymmetric carbon atoms and hence include various stereoisomers such as geometrical isomers, tautomers and optical isomers, either in admixture or isolated form. To

isolate and purify these stereoisomers, the skilled artisan may employ any ordinary techniques including optical resolution by preferential crystallization or column chromatography or asymmetric synthesis.

[0060]

The compounds (I) of the present invention occasionally form acid addition salts. Depending on the type of substituents, they also form salts with bases. While there are no particular limitations on the salts that can be formed as long as they are pharmaceutically acceptable, specific examples include: acid addition salts as with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid and phosphoric acid, organocarboxylic acids such as acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, formic acid, malic acid, tartaric acid, citric acid and mandelic acid, organosulfonic acids such as methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and 2-hydroxyethanesulfonic acid, and acidic amino acids such as aspartic acid and glutamic acid; salts with alkali metals or alkaline earth metals (e.g. sodium, potassium, magnesium, calcium and aluminum), and organic bases such as methylamine, ethylamine, ethanolamine, pyridine, lysine,

arginine and ornithine; and ammonium salts.

[0061]

Further, the present invention encompasses hydrates of the compounds (I), pharmaceutically feasible various solvates of the compounds, their polymorphs and the like. Needless to say, the present invention is not limited to the compounds described in the Examples to be set forth later but encompasses all aromatic compounds having cyclic amino groups as represented by the formula (I), and all pharmaceutically acceptable salts thereof.

[0062]

(Methods of Production)

The compounds of the present invention which are represented by the formula (I) can be produced by the methods described below. In the following Production Method 1, Production Method 2 and Production Method 3 and the explanation, the definitions of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, G_1, G_2, G_3, G_4, Q, X, Y, Z_1, Z_2, m and n in the formulae (I), (I)-a, (I)-b, (III), (IV)-a, (IV)-b, (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XV)-a to (XV)-e, (XVI), (XVII), (XVIII)-a, (XVIII)-b, (XIX), (XX), (XXI), and (XXII) are the same as the former definitions described above. The compounds of the present invention which are represented by the formula (I) and

salts thereof can be synthesized by Production Method 1, Production Method 2 and Production Method 3 starting from compounds represented by the formulae (III), (XV) and (XVI) or salts thereof which can be readily prepared from documented or commercial compounds.

[0063]

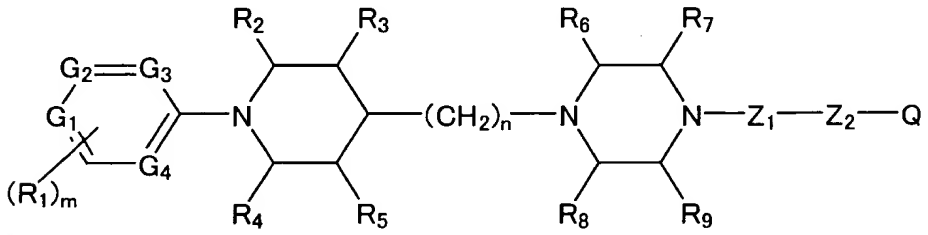
On the pages that follow, the methods of production of the compounds of the present invention are described in detail.

<Production Method 1>

A class of compounds of the formula (I) wherein X = CH and Y = N are represented by the formula (I)-a and the methods of producing them are described below.

[0064]

[Chemical Formula 7]

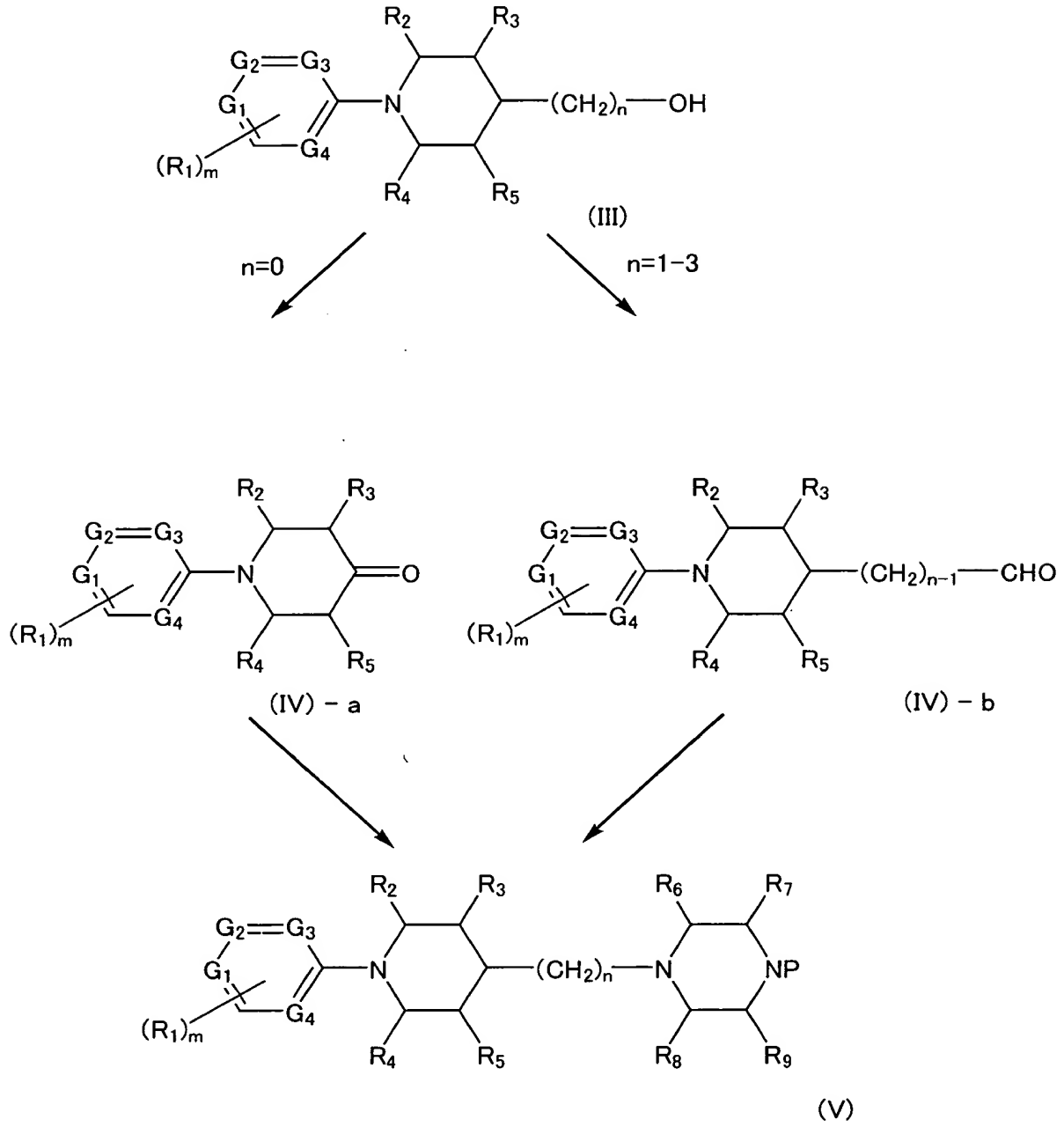


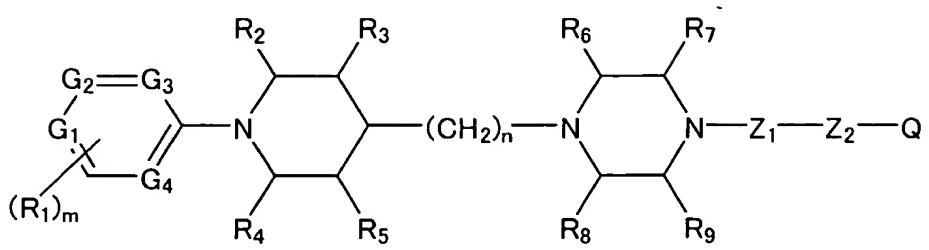
(I)-a

(wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, G_1, G_2, G_3, G_4, Q, Z_1, Z_2, m and n have the same meanings as defined above) are produced by the following methods. As described in Production Method 1-1,

[Chemical Formula 8]

Production Method 1-1



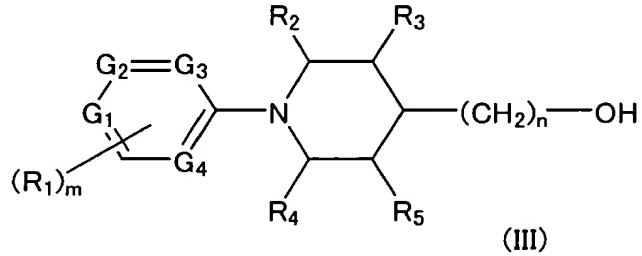


(I) - a

[0065]

A compound of the formula (III) which can be readily derived from a commercial product or a salt thereof:

[Chemical Formula 9]

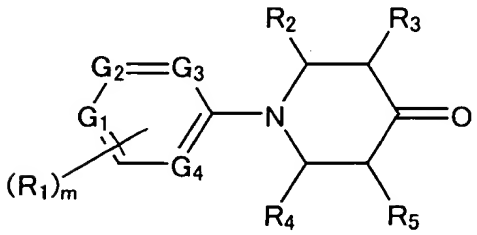


(III)

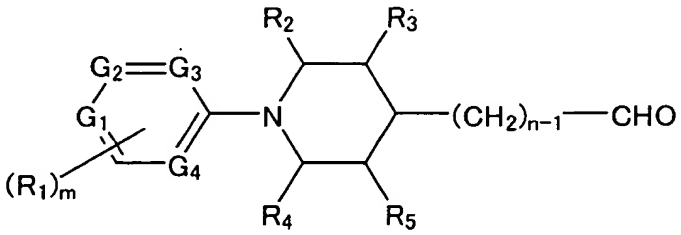
(wherein R_1, G_1 - G_4, R_2 - R_5, m and n have the same meanings as defined above) is subjected to an oxidation reaction, thereby producing a compound of the following formula (IV)-a or a salt thereof if n = 0 and a compound of the following formula (IV)-b or a salt thereof if n = 1 - 3:

[0066]

[Chemical Formula 10]



(IV) - a

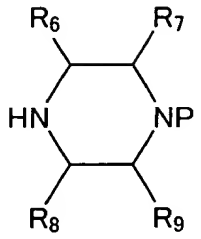


(IV) - b

(wherein R_1, G_1 - G_4, R_2 - R_5 and m have the same meanings as defined above). While the production method is described below in detail, it should be understood that the present invention is in no way limited to this method. The compound of the formula (III) or a salt thereof is subjected to an oxidation reaction such as the Swern oxidation (dimethyl sulfoxide (DMSO)/oxalyl chloride), oxidation with tetrapropylammonium perruthenate (TPAP)/N-methylmorpholine-N-oxide, the Corey-Kim oxidation (N-chlorosuccinimide (NCS)-dimethyl sulfide (DMS) complex), oxidation with pyridinium dichromate (PDC), oxidation with pyridinium chlorochromate (PCC) or the Jones oxidation ($Na_2Cr_2O_7$/Cr(VI)/sulfuric acid), preferably the Swern oxidation using DMSO/oxalyl chloride, in a halogenated hydrocarbon solvent typified by chloroform, methylene chloride and dichloroethane, preferably methylene chloride, at between -78°C and -60°C, preferably at between -78°C and -65°C, for a sufficient time to proceed the reaction to an adequate extent, specifically for 15 minutes to 1 hour, thereby the formula (IV)-a or the formula (IV)-b is derived. The compound of the formula (X):

[0067]

[Chemical Formula 11]

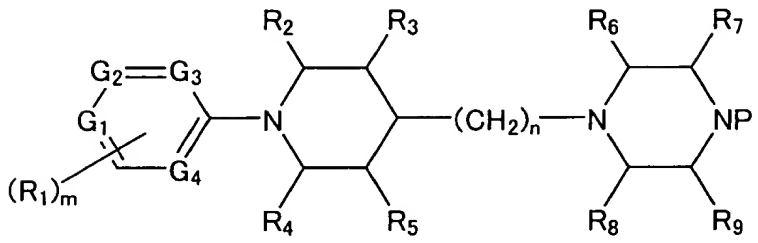


(X)

(wherein R_6 - R_9 have the same meanings as defined above; P is a secondary amino protecting group such as a carbamate typified by t-butoxycarbonyl and benzyloxycarbonyl, an amide typified by formyl, acetyl and benzoyl, or an alkyl typified by benzyl, allyl, trityl and methoxymetyl) are subjected to a reductive amination reaction with a reducing agent such as sodium triacetoxyborohydride, sodium borohydride, lithium borohydride, diisobutylaluminum hydride or sodium cyanoborohydride, in a halogenated hydrocarbon solvent typified by chloroform, methylene chloride and dichlroethane, preferably methylene chloride, in the presence or absence of acetic acid, preferably in its presence, under an argon atmosphere, between -78°C and room temperature, preferably under cooling with ice, for a sufficient time to proceed the reaction to an adequate extent, specifically for 3 - 12 hours, thereby the formula (VI) :

[0068]

[Chemical Formula 12]

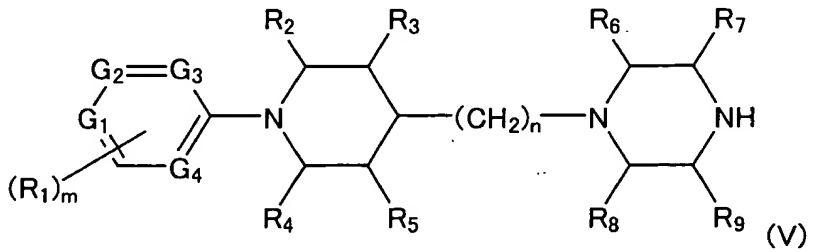


(VI)

(wherein R_1, G_1 - G_4, R_2 - R_9, P, m and n have the same meanings as defined above) is derived. The compound of the formula (VI) or a salt thereof is subjected to a deprotective reaction in the presence or absence of anisole, preferably in its presence, using an acid such as trifluoroacetic acid, hydrochloric acid, sulfuric acid, p-toluenesulfonic acid or methanesulfonic acid, preferably trifluoroacetic acid, under an argon atmosphere at a temperature between cooling with ice and room temperature, preferably at room temperature, for a sufficient time to proceed the reaction to an adequate extent, specifically for 3 - 12 hours, thereby the formula (V) or a salt thereof:

[0069]

[Chemical Formula 13]



(V)

(wherein R_1, G_1 - G_4, R_2 - R_9, m and n have the same meanings as defined above) is derived. A reactive halogenic derivative of the formula (XIII):

[0070]

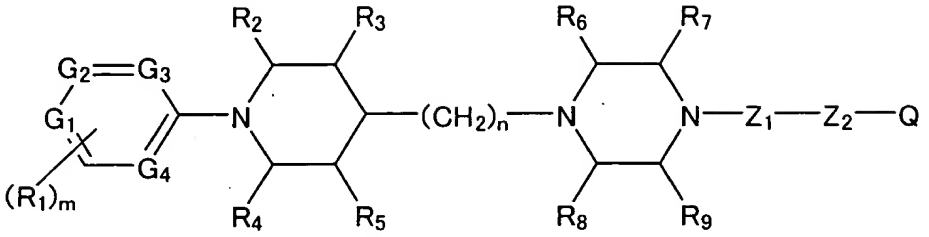
[Chemical Formula 14]

$$W\text{-}Z_1\text{-}Z_2\text{-}Q \qquad \text{(XIII)}$$

(wherein W is a halogen atom, a leaving group such as a methanesulfonyloxy group or a para-toluenesulfonyloxy group; Z_1, Z_2 and Q have the same meanings as defined above) are subjected to a reaction using an inorganic base such as potassium carbonate, cesium carbonate, calcium carbonate or sodium hydride or an organic base such as triethylamine, pyridine or N,N-dialkylaniline, preferably triethylamine, within a polar solvent such as acetonitrile or N,N-dimethylformamide (DMF), a halogenated hydrocarbon solvent typified by chloroform and methylene chloride or an ether-based solvent typified by ether and tetrahydrofuran (THF), preferably methylene chloride, under an argon atmosphere at a temperature between room temperature and boiling point of the solvent used, preferably at room temperature, for a sufficient time to proceed the reaction to an adequate extent, specifically for 1 - 12 hours, thereby producing a compound of the formula (I)-a or a salt thereof:

[0071]

[Chemical Formula 15]



(I)-a

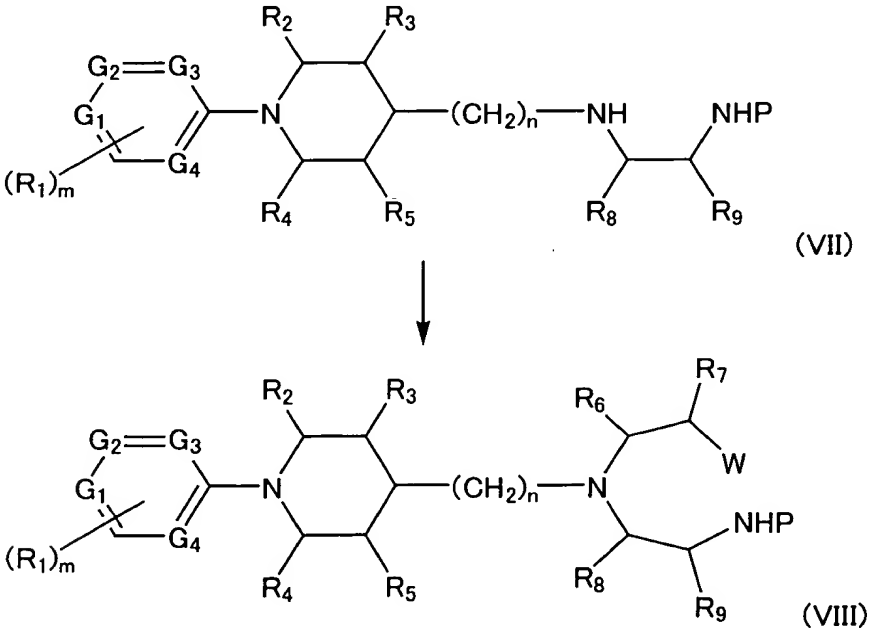
(wherein R_1, G_1 - G_4, R_2 - R_9, Q, Z_1, Z_2, m and n have the same meanings as defined above).

[0072]

Alternatively, the same compound can be produced by the procedure described in Production Method 1-2.

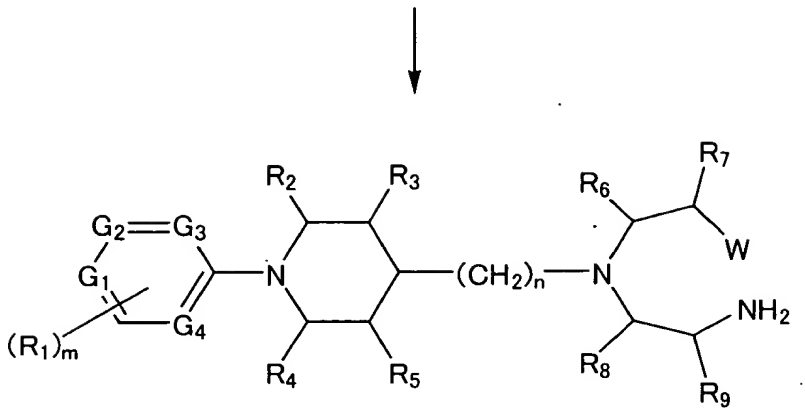
[Chemical Formula 16]

Production Method 1-2

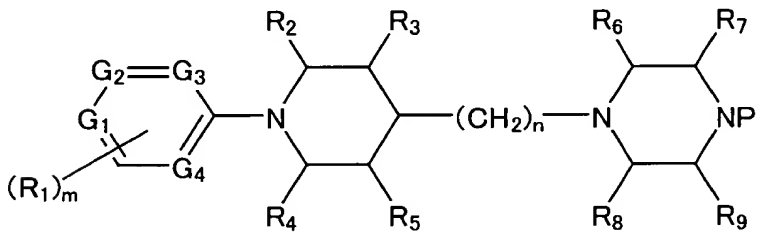


(VII)

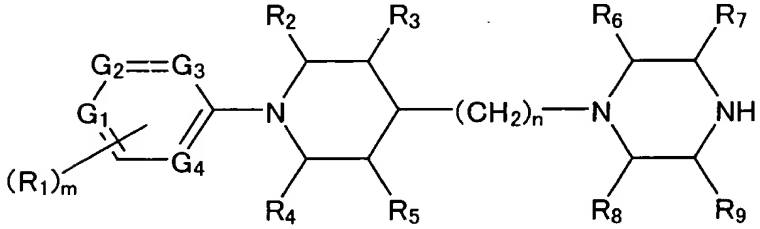
(VIII)



(IX)



(VI)

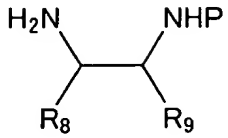


(V)

A compound of the formula (IV)-a or (IV)-b and a compound of the formula (XI):

[0073]

[Chemical Formula 17]

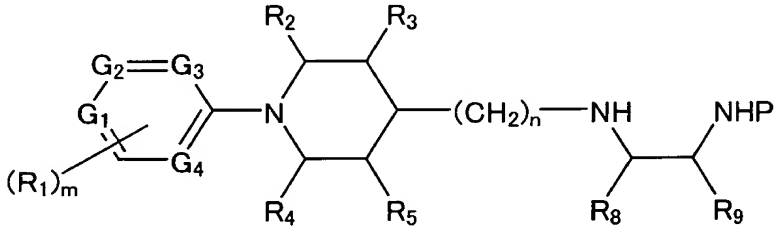


(XI)

(wherein R_8, R_9 and P have the same meanings as defined above) are reacted by the same procedure as the reaction of a compound of the formula (IV)-a or (IV)-b and the formula (X) to produce a compound of the formula (VI), the formula (VII):

[0074]

[Chemical Formula 18]

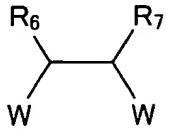


(VII)

(wherein G_1 - G_4, P, R_1 - R_5, R_8, R_9, m and n have the same meanings as defined above) is derived. A reactive halogenic derivative of the formula (XII):

[0075]

[Chemical Formula 19]



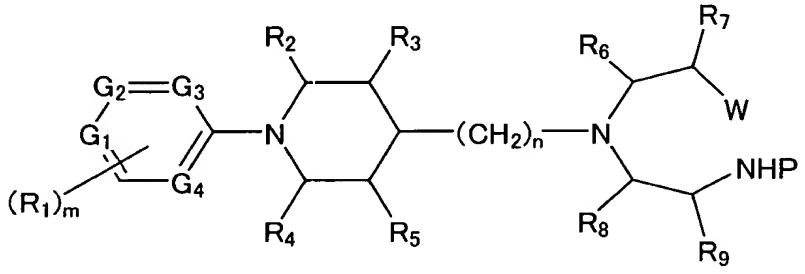
(XII)

(wherein R_6, R_7 and W have the same meanings as defined above) is subjected to a reaction using an inorganic base

such as potassium carbonate, cesium carbonate, calcium carbonate or sodium hydride or an organic base such as triethylamine, pyridine or N,N-dialkylaniline, preferably triethylamine, within a polar solvent such as acetonitrile or DMF, a halogenated hydrocarbon solvent typified by chloroform and methylene chloride or an ether-based solvent typified by ether or THF, preferably methylene chloride, under an argon atmosphere at a temperature between room temperature and boiling point of the solvent used, preferably at room temperature, for a sufficient time to proceed the reaction to an adequate extent, specifically for 1 - 12 hours, the formula (VIII):

[0076]

[Chemical Formula 20]

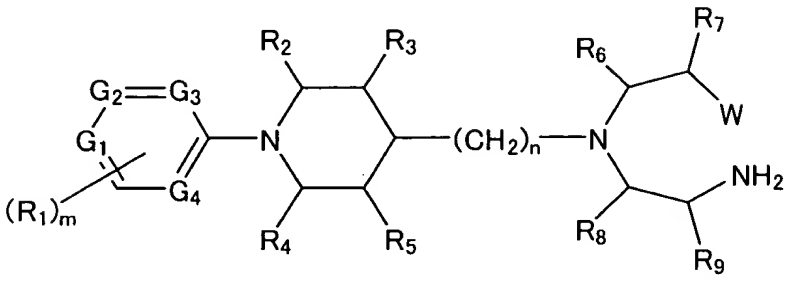


(XI)

(wherein R_1, G_1 - G_4, R_2 - R_9, P, W, m and n have the same meanings as defined above) is derived. From a compound of the formula (VIII), by the same procedure as the reaction of a compound of the formula (VI) to produce a compound of the formula (V), the formula (IX):

[0077]

[Chemical Formula 21]

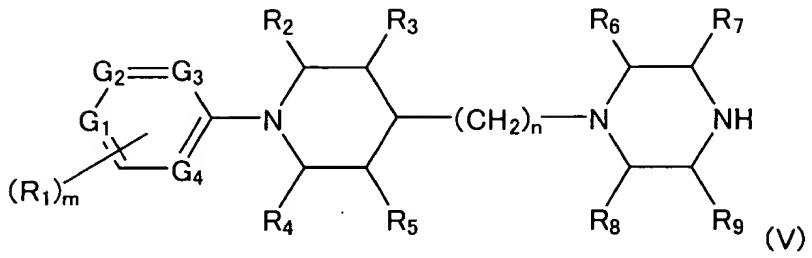


(IX)

(wherein R_1, G_1 - G_4, R_2 - R_9, W, m and n have the same meanings as defined above) is derived. A reactive halogenic derivative of the formula (IX) is subjected to a reaction using an inorganic base such as potassium carbonate, cesium carbonate, calcium carbonate or sodium hydride or an organic base such as triethylamine, pyridine or N,N-dialkylaniline, preferably triethylamine, within a polar solvent such as acetonitrile or DMF, a halogenated hydrocarbon solvent typified by chloroform and methylene chloride or an ether-based solvent typified by ether or THF, preferably methylene chloride, under an argon atmosphere at a temperature between room temperature and boiling point of the solvent used, preferably at room temperature, for a sufficient time to proceed the reaction to an adequate extent, specifically for 1 - 12 hours, the formula (V):

[0078]

[Chemical Formula 22]



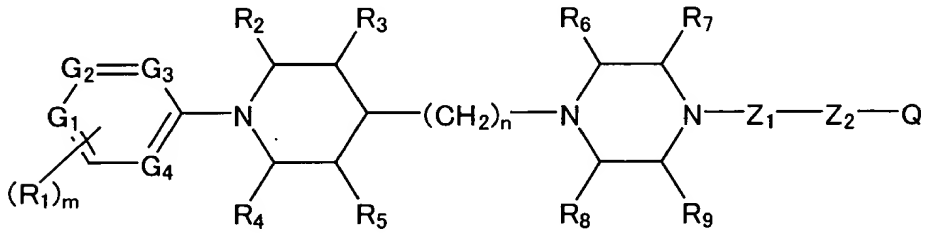
(V)

(wherein R_1, G_1 - G_4, R_2 - R_9, m and n have the same meanings as defined above) or a salt thereof is derived.

By the same procedure as described above, thereby producing the formula (I)-a:

[0079]

[Chemical Formula 23]



(I)-a

(wherein R_1, G_1 - G_4, R_2 - R_9, Q, Z_1, Z_2, m and n have the same meanings as defined above) or a salt thereof.

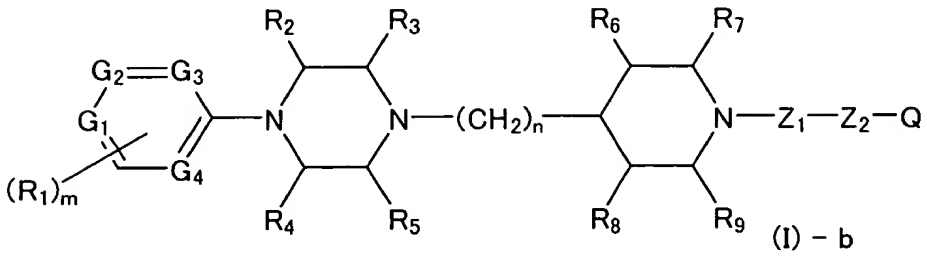
[0080]

<Production Method 2>

A class of compounds of the formula (I) wherein X = N and Y = CH are represented by the formula (I)-b and the methods of producing them are described below.

[Chemical Formula 24]

Compounds represented by

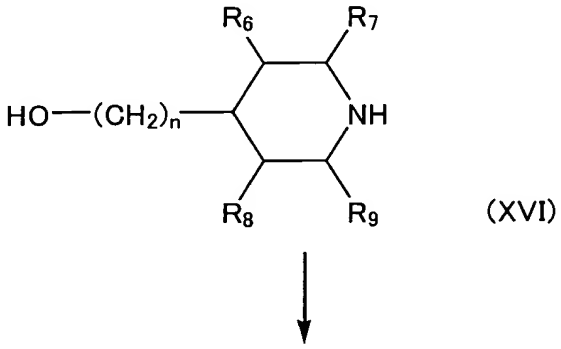


(I) - b

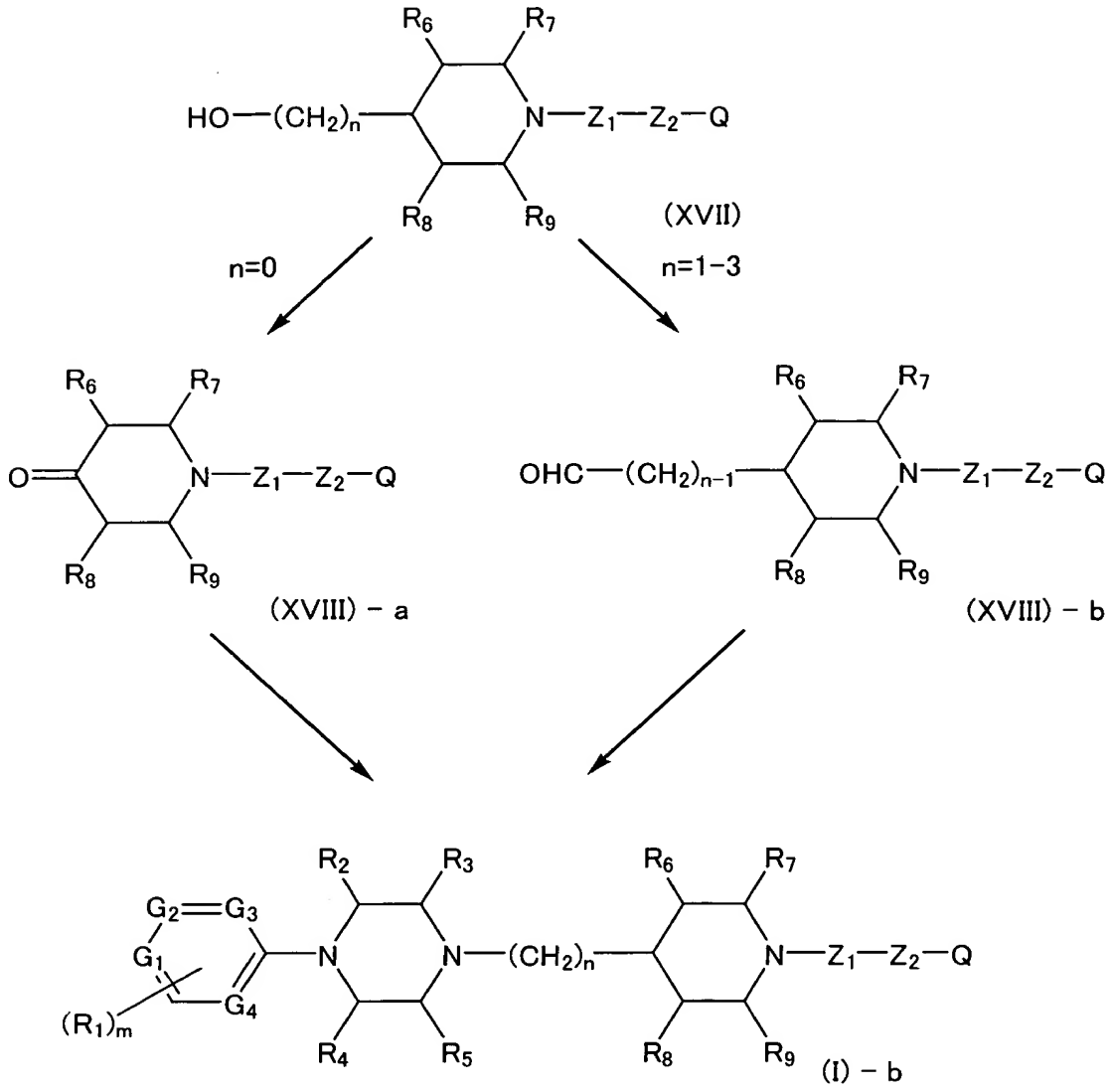
(wherein R_1, G_1 - G_4, Q, Z_1, Z_2, R_2 - R_9, m and n have the same meanings as defined above) are produced as described in Production Method 2-1.

[Chemical Formula 25]

Production Method 2-1



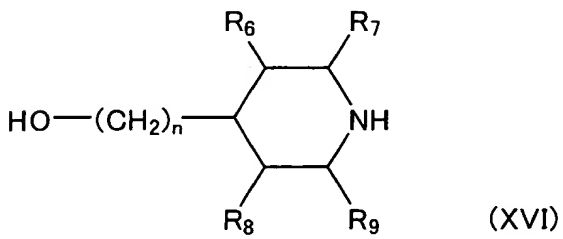
(XVI)



[0081]

A compound of the formula (XVI):

[Chemical Formula 26]



(wherein R_6 - R_9 and n have the same meanings as defined above), which is either commercially available or derived from commercial products by documented procedures, or a salt thereof is subjected to the same reaction as described above with a reactive halogenic derivative of the formula (XIII):

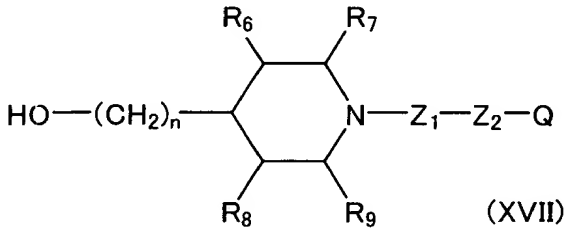
[Chemical Formula 27]

$$W\text{-}Z_1\text{-}Z_2\text{-}Q \qquad \text{(XIII)}$$

(wherein W is a halogen atom, a leaving group such as a paratoluenesulfonyloxy group; Z_1, Z_2 and Q have the same meanings as defined above), thereby producing a compound of the formula (XX) or a salt thereof:

[0082]

[Chemical Formula 28]

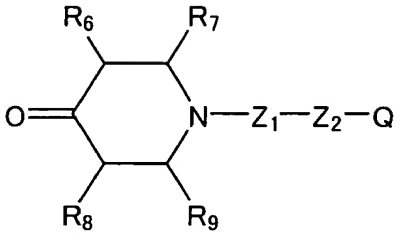


(XVII)

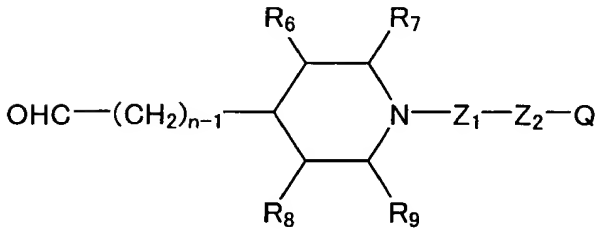
(wherein Q, Z_1, Z_2, n and R_6 - R_9 have the same meanings as defined above). The formula (XVII) or a salt thereof is subjected to the same reaction as the formula (III) to the formula (IV)-a or (IV)-b to produce a compound of the following formula (XVIII)-a if n = 0 and a compound of the following formula (XVIII)-b if n = 1 - 3:

[0083]

[Chemical Formula 29]



(XVIII) - a

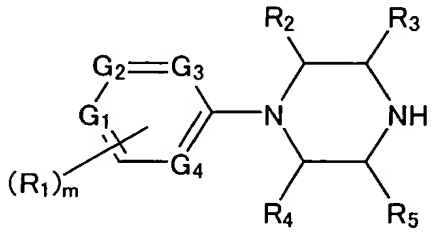


(XVIII) - b

(wherein Q, Z_1, Z_2, n and R_6 - R_9, have the same meanings as defined above). It is subjected to the same reductive amination reaction as described above with a compound of the formula (XX):

[0084]

[Chemical Formula 30]



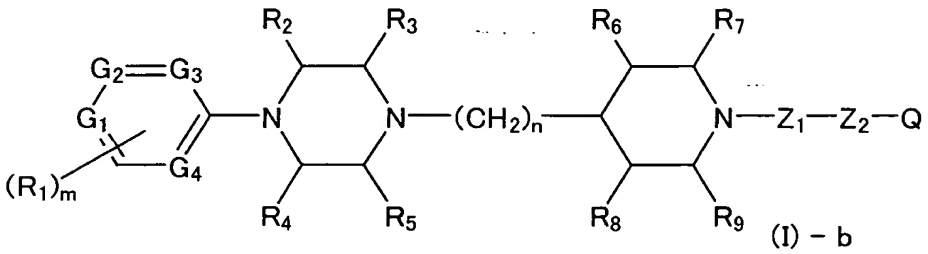
(XX)

(wherein R_1, G_1 - G_4, R_2 - R_5 and m have the same meanings as defined above) ,which is either commercially available or

derived from commercial products by documented procedures, to produce a compound of the formula (I)-b:

[0085]

[Chemical Formula 31]



(I) - b

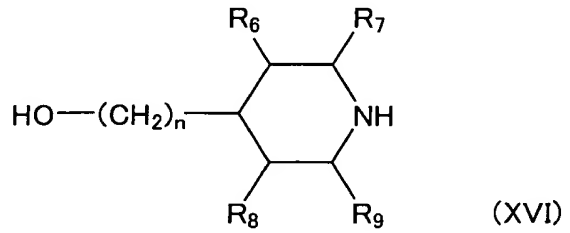
(wherein R_1, G_1 - G_4, Q, Z_1, Z_2, R_2 - R_9, m and n have the same meanings as defined above).

[0086]

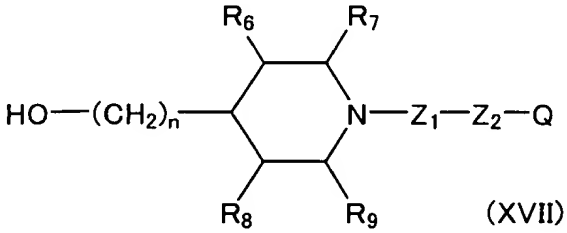
Alternatively, as described in Production 2-2,

[Chemical Formula 32]

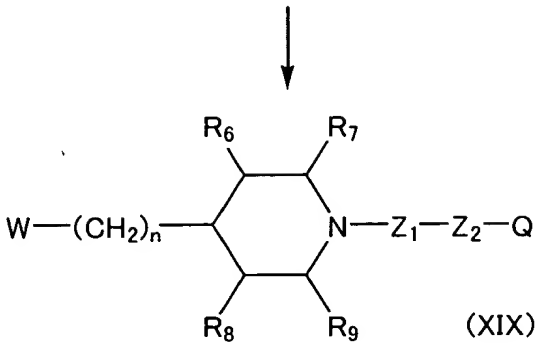
Production Method 2-2



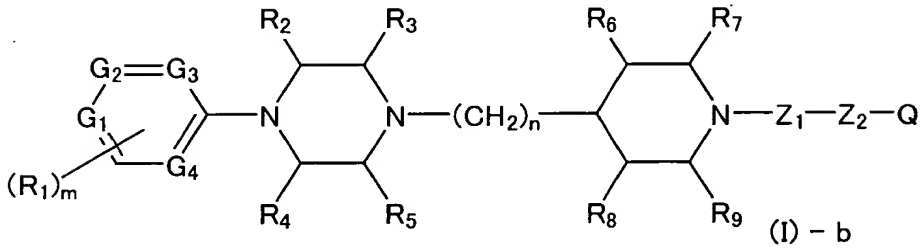
(XVI)



(XVII)



(XIX)

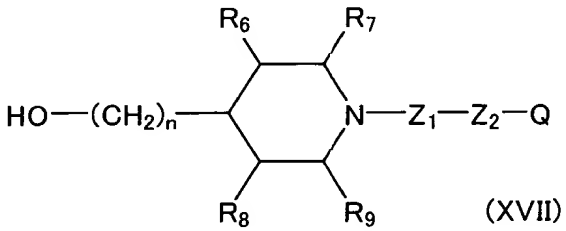


(I) - b

The compound of the formula (XVII) or a salt thereof:

[0087]

[Chemical Formula 33]



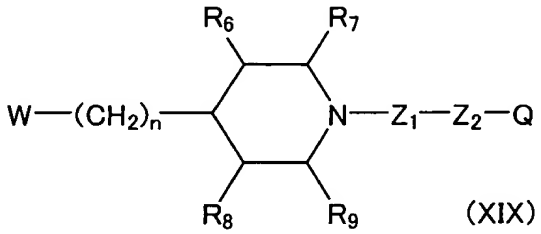
(XVII)

(wherein Q, Z_1, Z_2, n and R_6 - R_9 have the same meanings as defined above) that was produced by the same procedure as described above is subjected to reaction in a halogenated hydrocarbon solvent typified by chloroform, methylene chloride and dichloroethane, preferably methylene chloride, using thionyl chloride, phosphorus pentachloride,

phosphorus oxychloride, thionyl bromide, phosphorus pentabromide or phosphorus oxybromide, preferably thionyl chloride or thionyl bromide, at between -20°C and 50°C, preferably at between under cooling with ice and room temperature; alternatively, the same compound or a salt thereof is subjected to reaction in a solvent of carbon tetrachloride or carbon tetrabromide, using triphenylphosphine at a temperature between room temperature and the temperature where the solvent refluxes; or alternatively, the same compound or a salt thereof is subjected to reaction in an ether-based solvent such as ether or THF, preferably ether, using phosphorus trichloride or phosphorus tribromide, preferably phosphorus trichloride, at between -20°C and 50°C, preferably under cooling with ice; by either scheme, a compound of the formula (XIX) or a salt thereof:

[0088]

[Chemical Formula 34]



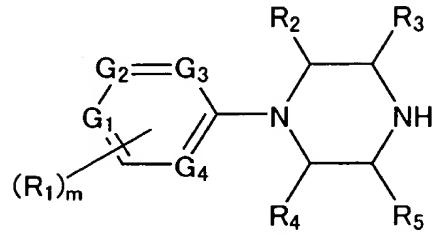
(XIX)

(wherein Q, W, Z_1, Z_2 n and R_6 - R_9 have the same meanings as defined above) is derived. The compound of the formula

(XX):

[0089]

[Chemical Formula 35]



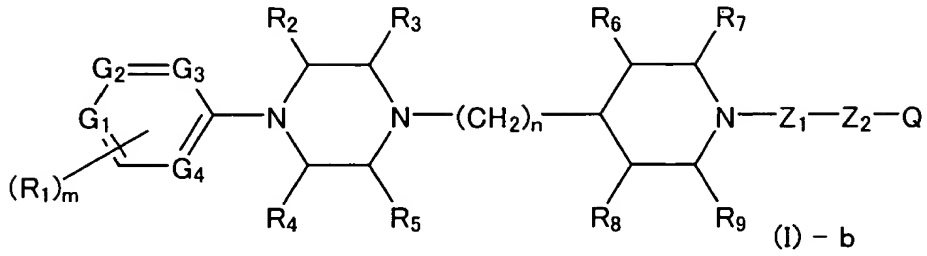
(XX)

(wherein R_1, G_1 - G_4, R_2 - R_5 and m have the same meanings as defined above) and a compound of the formula (XIX) that was obtained as described above are subjected to SN2 type reaction using an inorganic base such as potassium carbonate, cesium carbonate, calcium carbonate or sodium hydride or an organic base such as triethylamine, pyridine or N,N-dialkylaniline, preferably triethylamine, within a polar solvent such as acetonitrile or DMF, a halogenated hydrocarbon solvent typified by chloroform and methylene chloride or an ether-based solvent typified by ether and THF, preferably methylene chloride, under an argon atmosphere at a temperature between room temperature and boiling point of the solvent used, preferably at room temperature, for a sufficient time to proceed the reaction to an adequate extent, specifically for 1 - 12 hours,

[0090]

thereby producing a compound of the formula (I)-b:

[Chemical Formula 36]



(I) - b

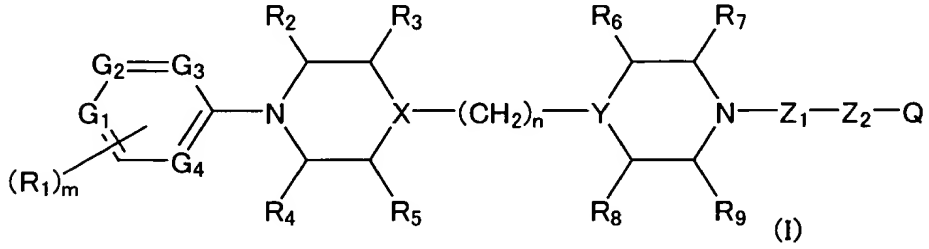
(wherein R_1, G_1 - G_4, Q, Z_1, Z_2, R_2 - R_9, m and n have the same meanings as defined above).

[0091]

<Production Method 3>

The compound of the formula (I):

[Chemical Formula 37]

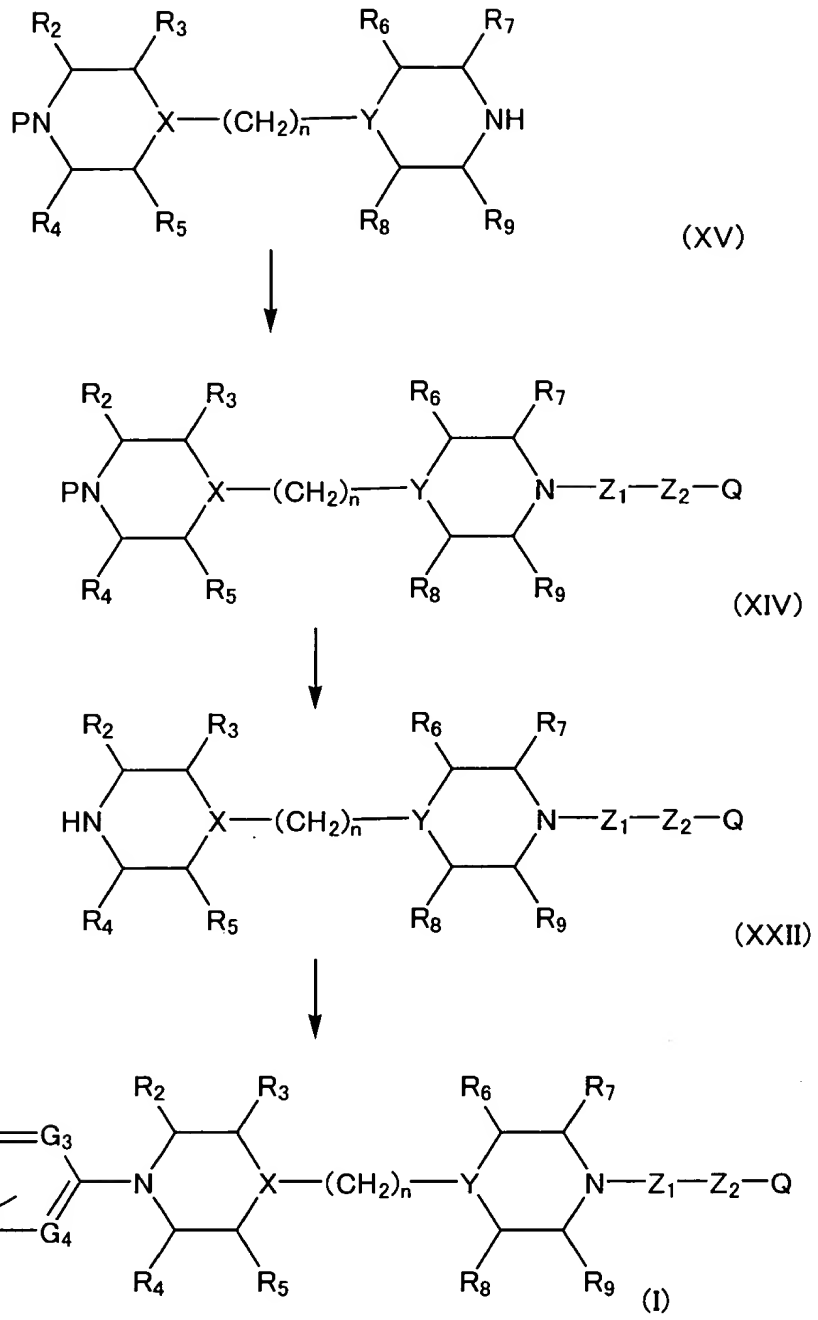


(I)

(wherein R_1, G_1 - G_4, Q, R_2 - R_9, X, Y, m, n, Z_1 and Z_2 have the same meanings as defined above) can also be produced by the following.

[Chemical Formula 38]

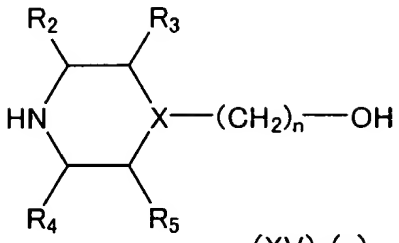
Production Method 3



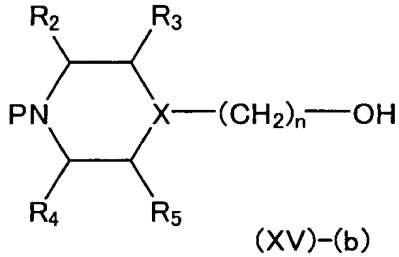
[0092]

The compound of the formula (XV)-(e), that can be produced from (XV)-(a) that is commercially available, or (XV)-(b):

[Chemical Formula 39]



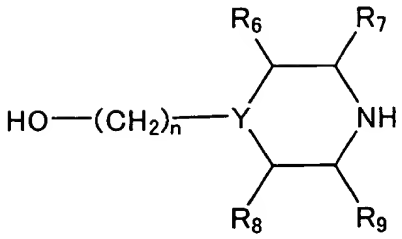
(XV)-(a)



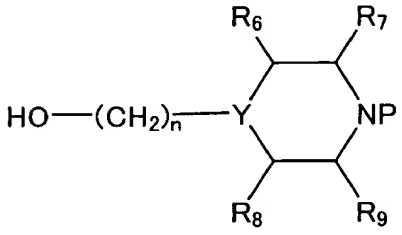
(XV)-(b)

(wherein R_2 - R_5, P, X and n have the same meanings as defined above) that is commercially available or readily derived from (XV)-(a) according to Production Method 1, or produced from (XV)-(c) that is commercially available, or (XV)-(d):

[Chemical Formula 40]



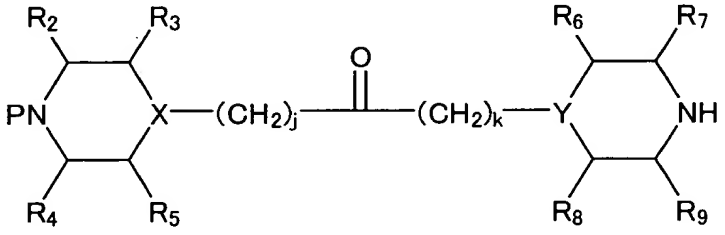
(XV)-(c)



(XV)-(d)

(wherein R_6 - R_9, P, Y and n have the same meanings as defined above) that is commercially available or readily derived from (XV)-(c) according to Production Method 2, or prepared by a documented (WO96/10022) method,:

[Chemical Formula 41]

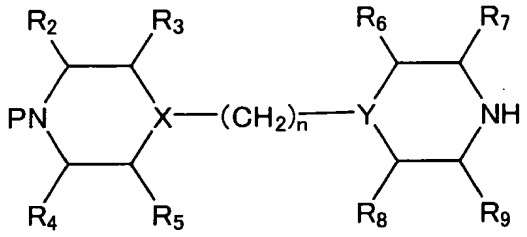


(XV)-(e)

(wherein R_2 - R_9, P, X and Y have the same meanings as defined above; j and k are each an integer of 0 - 2; the total number of carbon atoms in the bridge between the two rings is 1 - 3) is subjected to a reduction reaction in an ether-based solvent typified by ether, THF, DME and diglyme

(diethylene glycol dimethyl ether), preferably THF, under an argon atmosphere using a reducing agent such as lithium aluminum hydride, diisobutyl aluminum hydride, borane dimethyl sulfide complex, borane THF complex, borane trimethylamine complex or alane at a temperature between -78°C and the temperature where the solvent refluxes, for a sufficient time to proceed the reaction to an adequate extent, specifically for 1 - 12 hours, thereby producing a compound of the formula (XV):

[Chemical Formula 42]



(XV)

(wherein R_2 - R_9, P, X, Y and n have the same meanings as defined above). The compound of the formula (XV) and reactive halogenic derivatives of the formula (XIII):

[Chemical Formula 43]

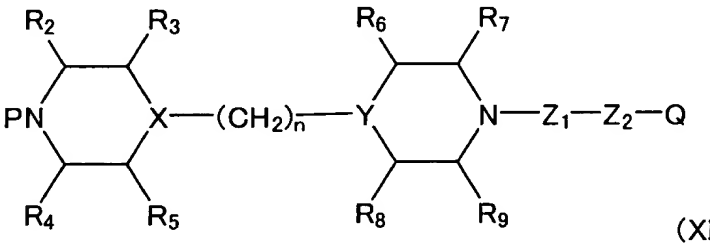
$$W\text{-}Z_1\text{-}Z_2\text{-}Q \qquad \text{(XIII)}$$

(wherein W, Z_1, Z_2 and Q have the same meanings as defined above), are subjected to reaction using an inorganic base such as potassium carbonate, cesium carbonate, calcium carbonate or sodium hydride or an organic base such as triethylamine, pyridine or N,N-dialkylaniline, preferably

triethylamine, within a polar solvent such as acetonitrile or N-dimethylformamide (DMF), a halogenated hydrocarbon solvent typified by chloroform and methylene chloride or an ether-based solvent typified by ether and tetrahydrofuran (THF), preferably methylene chloride, under an argon atmosphere at a temperature between room temperature and boiling point of the solvent used, preferably at room temperature, for a sufficient time to proceed the reaction to an adequate extent, specifically for 1 - 12 hours; thereby producing a compound of the formula (XIV) or a salt thereof:

[0093]

[Chemical Formula 44]



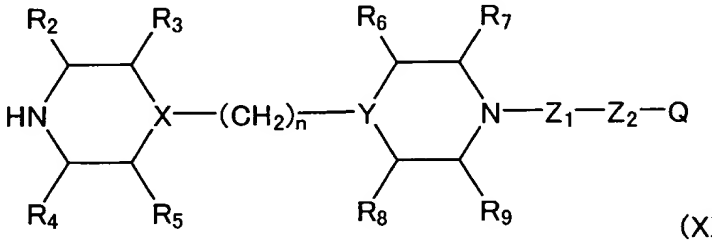
(XIV)

(wherein R_2 - R_9, P, Z_1, Z_2, Q, X, Y and n have the same meanings as defined above). The compound of the formula (XIV) or a salt thereof is subjected to a deprotective reaction in the presence or absence of anisole, preferably in its presence, using an acid such as trifluoroacetic acid, hydrochloric acid, sulfuric acid, p-toluenesulfonic acid or methanesulfonic acid, preferably trifluoroacetic acid,

under an argon atmosphere at a temperature between under cooling with ice and room temperature, preferably at room temperature, for a sufficient time to proceed the reaction to an adequate extent, specifically for 3 - 12 hours, thereby producing a formula (XXII) or a salt thereof:

[0094]

[Chemical Formula 45]



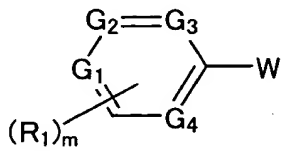
(XXII)

(wherein R_2 - R_9, Z_1, Z_2, Q, X, Y and n have the same meanings as defined above).

The compound of the formula (XXII) or a salt thereof and a compound of the following formula (XXI) that is either commercially available or derived from a commercial product by documented methods:

[0095]

[Chemical Formula 46]



(XXI)

(wherein R_1, G_1 - G_4, W and m have the same meanings as defined above) are subjected to reaction in the presence of

a copper powder, copper oxide or an iron powder, preferably in the presence of a copper powder, using an inorganic base such as potassium hydroxide, sodium hydroxide or potassium carbonate or an alkali metal agent such as sodium alkoxide or sodium hydroxide, preferably potassium carbonate, either in the absence of a solvent or in the presence of a suitable high-boiling point solvent such as DMF, DMSO, DME, dibutyl ether, xylene, decalin, or 1,3-dimethyl-2-imidazolidone (DMI), preferably in its absence, at a temperature between 100°C and 200°C, preferably between 180°C and 190°C, for a sufficient time to proceed the reaction to an adequate extent, specifically for 1 - 12 hours.

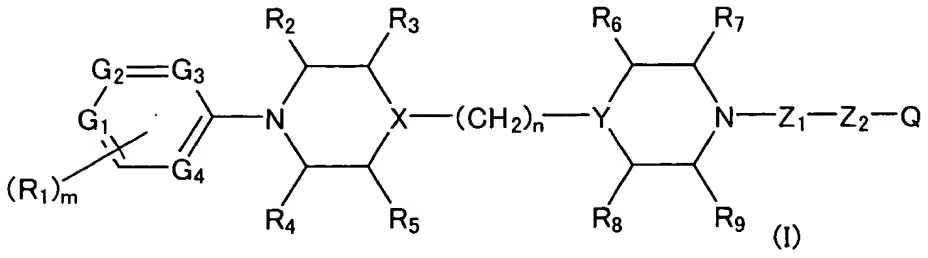
Depending on the case, a metal such as palladium or bismuth may be used to form a complex with the above-mentioned compound (XXVIII) so that the activity of the compound is enhanced before it is subjected to the above reaction.

[0096]

By the above-described method, one can produce the formula (I):

Formula (I)

[Chemical Formula 47]



(I)

(wherein R_1, G_1 - G_4, R_2 - R_9, Q, X, Y, m, n, Z_1 and Z_2 have the same meanings as defined above).

[0097]

If some of the substituents in the compounds to be synthesized in the above-described Production Method 1 to 3 are reactive groups such as a hydroxyl group, an amino group, a carboxyl group and a thiol group, these groups may be protected as appropriate in each reaction step, with the protective groups being removed at suitable stages. Protective groups may be introduced and removed as appropriate for the types of the groups to be protected and the prctective groups used; reference may be had to the Review section of "Protective Groups in Organic Synthesis", 2nd Edition, 1991.

[0098]

We now describe the pharmaceutical compositions of the present invention. The pharmaceutical compositions of the present invention may contain at least one compound of the general formula (I) (as already defined above) as an active ingredient and they may also contain a pharmaceutically

acceptable carrier. The preferred examples of the compounds of the general formula (I) have been described above.

The compounds of the present invention possess a potent an inhibitory activity of activated blood coagulation factor X. Hence, the compositions of the present invention are a potent an inhibitor of activated blood coagulation factor X, more particularly a specific inhibitor of activated blood coagulation factor X. The compositions are also an orally administrable inhibitor of activated blood coagulation factor X, as well as an orally administrable specific inhibitor of activated blood coagulation factor X. While there are many serine proteases, the activity of activated blood coagulation factor X is specifically inhibited by the compounds of the present invention and potently. They do not inhibit trypsin or chymotrypsin in substance, nor do they inhibit thrombin which is another serine protease in the blood coagulation cascade. Hence, the compounds of the present invention solve the aforementioned problems with the conventional thrombin inhibitors, for example, the tendency to cause bleeding. As further advantages, the compounds of the present invention can be rapidly absorbed by the digestive tract after oral administration, and they

therefore have high value of use as an oral drug.

[0099]

The compositions containing the compounds of the present invention can be used as preventives and/or therapeutics of diseases for which the FXa inhibitor is indicated. The compositions containing the compounds of the present invention can also be used as an anticoagulant, and as preventives and/or therapeutics of diseases for which the anticoagulant is indicated.

[0100]

In short, these drugs are effective in the prevention and/or treatment of diseases caused by thrombus or embolus. To mention specific examples of such diseases, they include: diseases from ischemic cerebrovascular disorders such as cerebral thrombosis, cerebral infarction, cerebral embolism, transient cerebral ischemic attacks (TIA) and cerebrovascular contractions after subarachnoid hemorrhage; diseases associated with ischemic heart diseases such as acute or chronic myocardial infarction, unstable angina pectoris and coronary thrombolysis; diseases from pulmonary infarction, pulmonary embolism and pulmonary angiopathy; and diseases from various cases of angiopathy including peripheral arterial obstruction, deep venous thrombosis, disseminated intravascular coagulation (DIC), thrombosis

after artificial blood vessel or heart valve replacement, reocclusion and restenosis following coronary artery bypass surgery, reocclusion and restenosis on or after PTCA, and thrombosis on extracorporeal circulation of blood. The drugs find particular use in the prevention of embolism, preferably the onset of cerebral embolism, that accompanies atrial fibrillation, heart valve replacement or valvular heart disease, the prevention of transient cerebral ischemic attacks, especially their recurrence, and in the prevention and treatment of deep venous thrombosis or DIC.

[0101]

If the drugs of the present invention are to be used as pharmaceuticals, administering them for the purpose of preventing the above-mentioned diseases is recommended and particularly important. The drugs of the present invention are not direct acting thrombolytic agents nor are they direct platelet agglutination inhibiting agents. Hence, they are preferably administered for preventive purposes to patients predisposed to thrombus formation or patients having the risk factor of thrombosis and embolism. In particular, patients who have atrial fibrillation, patients who underwent heart valve replacement and patients suffering from valvular heart disease have the high risk of thrombus formation in the lesions or the area of

transplantation, which often triggers the development of cerebral infarction and the occurrence of fatal attacks is by no means rare. The drugs of the present invention are expected to prove extremely useful in preventing the induced thrombus or embolus formation in such patients, most preferably for preventing the onset of cerebral infarction.

Therapy on the above-mentioned conditions is performed over a prolonged period. The drugs of the present invention can be administered perorally, have less side effects such as bleeding, need no frequent monitoring and hence can be used safely for a prolonged time.

[0102]

In other words, the drugs of the invention are preventives and/or therapeutics of embolus that accompanies atrial fibrillation, heart valve replacement or valvular heart disease. Preferably, they are preventives of the onset of cerebral embolism that accompanies these events. They are also preventives and/or therapeutics of transient cerebral ischemic attacks. In particular, they are preventives of the recurrence of the disease. They are also preventives and/or therapeutics of DIC.

[0103]

The compositions containing the compounds of the

present invention as an active ingredient are also effective as veterinary drugs and have high value of use. They are also useful in the measurement of various functional parameters in blood coagulation or as reagents in laboratories.

Since the compounds of the present invention have FXa inhibitory action, the compositions containing them can also be used as a preventive or therapeutic of the infection with influenza virus due to their activity in inhibiting the growth of the virus.

[0104]

Next, the outstanding FXa inhibitory activity of the compounds of the present invention can be verified by the following tests.

1) Measuring human FXa inhibitory activity

In vitro FXa inhibitory activity is measured according to the method of Kettner et al., J. Biol. Chem., 1990, 265, 18289-18297. That is Human FXa (Enzyme Research Laboratories, Inc., 0.019 U/ml) is mixed with a test compound diluted with dimethyl sulfoxide (DMSO) at various concentrations and a synthetic substrate S-2222 (Chromogenix AB, 0.4 mM) and incubated in a Tris-HCl buffer (pH 7.5) at 37 °C. The absorbance at 405 nm is measured continuously. To calculate the FXa inhibitory activity of

the test compound, the initial reaction velocity is compared with the value for a control containing no test compound. The FXa inhibitory activity of a test compound is usually expressed as IC_{50}.

[0105]

The compounds of the present invention were measured for their FXa inhibitory activity by the above-described method and they had potencies between 0.1 nM and 1μM in terms of IC_{50}. The control compound in the assay system was 1-((E)-4-chlorostyrylsulfonyl)-4-[1-(4-pyridyl)piperidin-4-ylcarbonyl]piperazine (the compound synthesized in Example 39-2b of WO96/10022) and it had an IC_{50} of 150 nM. The compounds synthesized in the Examples of the present invention had FXa inhibitory activities at least equal to that of the control compound.

[0106]

2) Measurement of Anticoagulation Activity

a) Measuring exogenous coagulation time

Thromboplastin time (PT) is measured in the presence of test compounds diluted at various concentrations. A test compound diluted with DMSO at various concentrations is mixed with human plasma and incubated at 37°C for 3 minutes. Then, a thromboplastin reagent is added and the coagulation time is measured. The anticoagulation activity

of the test compound is indicated in terms of the concentration required to double the coagulation time for the case where no test compound is added. In the actual test, the compounds of the present invention were found to be effective in extending the PT.

[0107]

b) Measuring endogenous coagulation time

Activated partial thromboplastin time (APTT) is measured in the presence of test compounds diluted at various concentrations. A test compound diluted with DMSO at various concentrations is mixed with human plasma and APTT reagent and incubated at 37°C for 2 minutes. Then, a calcium chloride (25 mM) is added and the coagulation time is measured. The anticoagulation activity of the test compound is indicated in terms of the concentration required to double the coagulation time for the case where no test compound is added. In the actual test, the compounds of the present invention were found to be effective in extending the APTT.

[0108]

3) *Ex vivo* anticoagulant studies in rats (i.v.)

Male Wistar rats (200 - 300 g; SLC, Inc.) that have been starved for more than 12 hours are administered through a femoral vein with a single dose of a drug

dissolved in physiological saline (or 10% DMSO solution) and blood is collected at given time intervals in 1/10th volume of 3.8% sodium citrate and centrifuged at 3000 rpm for 10 minutes to separate plasma, which is used in the following measurement a) and b) of exogenous coagulation time (PT) and endogenous coagulation time (APTT).

[0109]

a) exogenous coagulation time (PT)

A 50-μl portion of the plasma is incubated at 37°C for 3 minutes and a thromboplastin solution (100 μl) is added to start coagulation. The coagulation time is measured. In the actual test, the intravenously administered compounds of the present invention were found to be effective in extending the PT.

[0110]

b) endogenous coagulation time (APTT).

A 50-μl portion of the plasma is mixed with an APTT reagent (50 μl) and incubated at 37°C for 2 minutes and a 25 mM calcium chloride solution (50 μl) is added to start coagulation. The coagulation time is measured.

In the actual test, the intravenously administered compounds of the present invention were found to be effective in extending the APTT.

[0111]

4) *Ex vivo* anticoagulant studies in rats (p.o.)

The test 3) was repeated, except that the administration of a single dose through a femoral vein was replaced by forced peroral administration via an oral probe. At given time intervals, blood was collected in 1/10th volume of 3.8% sodium citrate. As in the test 3), exogenous coagulation time and endogenous coagulation time were measured.

In this test 4), the compounds of the present invention were found to be effective in extending the coagulation time upon oral administration.

[0112]

All that is required for the pharmaceutical compositions of the present invention is that they contain at least one of the compounds of the general formula (I) (as already defined above) as an active ingredient. They may also contain any pharmaceutically acceptable carriers. The preferred examples of the compounds of the general formula (I) have already been mentioned.

[0113]

As described above, the compounds of the present invention show a potent FXa inhibitory activity and they have high specificity since they do not inhibit trypsin, chymotrypsin or thrombin. Measuring the PT and APTT time,

the compounds of the present invention have the intended anticoagulation action without the risk of excessive bleeding tendency. As a further advantage, their action is exhibited in vivo and upon oral administration. And high safety is assured.

[0114]

To prevent or treat the various diseases mentioned hereinabove, the compounds of the present invention may be administered either individually or in combination with other pharmacologically active ingredients. Exemplary pharmacologically active ingredients include: known anticoagulating agents [e.g. tissue plasminogen activator (t-PA) and its derivatives (inclusive of modified products and derivatives of the so-called "second generation"), urokinase, streptokinase and thrombomodulin]; known platelet agglutination inhibitors (e.g. aspirin, thromboxane antagonist, thromboxane synthesis inhibitor and GPIIb/IIIa inhibitor); known therapeutics of hyperlipidemia (e.g. clofibrate and related drugs, HMG-CoA inhibitor and EPA-E); and known antihypertensives (e.g. nifedipine and diltiazem). The term "combination" as used herein covers not only the administration of a combination drug containing both the compound of the present invention and another pharmacologically active ingredient but also the

case where the two are in separate dosage forms and administered either at a time or at different times. The mode of administration is in no way limited as long as the compound of the present invention and another pharmacologically active ingredient exist simultaneously in the patient's blood.

[0115]

A pharmaceutical composition containing one or more of the compounds of the present invention and pharmaceutically acceptable salts thereof as an active ingredient may be formulated as capsules, pills, tablets, granules, subtilized granules and powders, drugs for internal application such as suspensions, emulsions, limonades, elixirs and syrups, as well as injections, nasal inhalants, suppositories, ointments and plasters using common pharmaceutical carriers, vehicles and other additives and thereafter applied to man and other animals either perorally or parenterally.

[0116]

The clinical dose at which the compounds of the present invention are to be administered to humans is determined as appropriate in consideration of various factors such as the symptoms of the patient to be treated, his or her body weight, age and sex; the usual daily dose

for an adult ranges from 0.1 mg to 1000 mg, preferably from 1 mg to 300 mg (for oral administration), and from 0.01 mg to 300 mg, preferably from 0.1 mg to 100 mg (for parenteral administration), which is administered either at a time or in divided portions. The dose is variable under actual conditions and smaller doses may sometimes suffice.

[0117]

The solid compositions to be administered perorally according to the present invention may be formulated as capsules, pills, tablets, powders, granules, etc. In these solid compositions, one or more active ingredients are combined with at least one inert carrier. Specific examples of inert carriers include vehicles (e.g. lactose, sucrose, mannitol, glucose, hyroxypropyl cellulose, microcrystalline cellulose and metasilicates), binders (e.g. crystalline cellulose, saccharides, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone and macrogol), lubricants (e.g. magnesium stearate, calcium stearate and talc), disintegrators (e.g. corn starch, carboxymethyl cellulose and cellulosic calcium glycolate), stabilizers (e.g. sugar alcohols and saccharides such as lactose), solubilizers or solvent promoters (e.g. cholesterol, triethanolamine, glutamic acid and aspartic acid), coloring agents, flavoring agents,

antiseptics, isotonization agents, dispersing agents, antioxidants (e.g. ascorbic acid and butyl hydroxyanisole), buffers, and preservatives (e.g. paraben and benzyl alcohol). If necessary, tablets, pills, granules and the like may have gastric or enteric film coatings formed of sucrose, gelatin, hydroxyproopylmethyl cellulose phthalate, etc.

[0118]

Injections for parenteral administration include sterilized aqueous or non-aqueous solutions, suspensions and emulsions. Carriers for aqueous solutions and suspensions include, for example, distilled water for injection and physiological saline. Carriers for non-aqueous solutions and suspensions include, for example, propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohols such as ethyl alcohol, and polysorbate 80 (trade name). These compositions may further contain the additives exemplified above, for example, isotonization agents, antiseptics, moistening agents, emulsifiers, dispersing agents, stabilizers, solubilizers and solvent promoters. These compositions are sterilized by suitable techniques such as passage through a membrane filter, incorporation of sterilizers and irradiation with uv light. Sterile solid compositions may

also be prepared and formulated as an injection that is dissolved, emulsified or suspended just prior to use. If the compounds of the present invention have low solubility, they may be subjected to a solubilizing treatment. Several solubilizing methods are known to be applicable to pharmaceutical preparations and they include the addition of surfactants (e.g. polyoxyethylene hydrogenated castor oils, higher aliphatic acid esters of polyoxyethylene sorbitan and aliphatic acid esters of sucrose), and the formation of solid dispersions from the drug and solubilizers such as high-molecular weight compounds (e.g. water-soluble polymers such as polyethylene glycol (PEG), hydroxypropylmethyl cellulose (HPMC) and polyvinyl pyrrolidone (PVP), and enteric polymers such as hydroxypropylmethyl cellulose phthalate (HPMCP) and methyl methacrylate-methacrylic acid copolymer (Eudragit L, S (TM); Rohm and Haas). If necessary, inclusion compounds may be formed using α-, β- or γ-cyclodextrin or hydroxypropyl cyclodextrin. These solubilizing methods may be modified as appropriate for the intended drug by having reference to literature such as "Yakugaku Monogurafu No. 1, Seibutsukagaku Riyono (Series of Monographs on Pharmacy, No. 1, Biochemical Availability)", Koji Nagai et al., Soft Science, 78-82 (1988) and "Saikin no Seizaigijutsu to Sono

Oyo (Recent Advances in Pharmaceutical Formulation Technology and Its Applications)", Isamu Utsumi, Iyaku Journal, 157-159 (1983). Among the methods mentioned above, the formation of a solid dispersion from the drug and a solubilizer to enhance its solubility is recommended [Japanese Patent Application Laid-Opened No. 49314/1981 and FR 2460667].

[0119]

Pharmaceutical Preparations

The following are representative examples of the pharmaceutical compositions of the present invention. In the description, Compound M means the compound of the present invention which is represented by the formula (I) or a pharmaceutically acceptable salt thereof; specifically, it is any one of the compounds synthesized in the Examples that follow.

(a) Capsule (50 mg)

Compound M	100 g
Lactose	398.5 g
Magnesium stearate	1.5 g

Weighed amounts of the above ingredients were mixed uniformly and the resulting powder mixture was filled in 250-mg portions into hard capsules of JP No. 1.

[0120]

(b) Tablet (1 mg)

Compound M	1.0 g
Lactose	92.2 g
Carboxymethylcellulose sodium	5.0 g
Corn starch paste (5% W/V paste)	0.8 g
Magnesium stearate	1.0 g

Weighed amounts of the above ingredients were compressed into tablets in the usual manner, each weighing 100 mg.

[0121]

(c) Tablet (10 mg)

Compound M	10 g
Lactose	160 g
Croscarmellose sodium	4.0 g
Corn starch	20.7 g
Polyvinyl pyrrolidone	2.3 g
Magnesium stearate	3 g

Weighed amounts of the above ingredients were compressed into tablets in the usual manner, each weighing 200 mg. The tablets were then enteric-coated with cellulose acetate phthalate.

[0122]

(d) Tablet (100 mg)

Compound M	100 g

Lactose	181.5 g
Croscarmellose sodium	12 g
Corn starch (5% W/V paste)	3.5 g
Magnesium stearate	3 g

Weighed amounts of the above ingredients were compressed into tablets in the usual manner, each weighing 300 mg.

[0123]

(e) Injection (0.1 mg/ml)

Compound M	0.1 W/V
Sodium phosphate buffered solution	2.3 % W/V
Citric acid	0.4%
Macrogol 400	3.5%
Water for injection	q.s. to make 100%

The above ingredients were mixed into solution and 1-ml portions of the solution were filled into injection ampules to make injections.

[0124]

(f) Injection (1.0 mg/ml)

Compound M	1.0% W/V
Sodium phosphate buffered solution	3.6% W/V
1 M Sodium hydroxide solution	15% W/V
Water for injection	q.s. to make

100%

The above ingredients were mixed into solution and 1-ml portions of the solution were filled into injection ampules to make injections.

[0125]

(g) Injection (50 mg/ml)

Compound M	5% W/V
1 M Sodium hydroxide solution	15% W/V
Macrogol 400	4.5%
0.1 M Hydrochloric acid	q.s.
Water for injection	q.s. to make 100%

The above ingredients were mixed into solution and 1-ml portions of the solution were filled into injection ampules to make injections.

[0126]

[Examples]

The following examples are provided for the purpose of further illustrating the present invention but are in no way to be taken as limiting.

Nuclear magnetic resonance (NMR) spectra were taken with JEOL JNM-EX270 FT-NMR (JEOL LTD.) or JEOL JNM-LA300 FT-NMR (JEOL LTD.; data marked with an asterisk); and high-resolution mass spectra (HRMS) were taken with JEOL JMS-

GCMATE (JEOL LTD.).

[0127]

Example 1 Synthesis of 1-[1-((E)-4-chlorostyrylsulfonyl)piperidin-4-yl]-4-(4-pyridyl)piperazine

<Step 1> Synthesis of 4-[1-((E)-4-chlorostyrylsulfonyl)]piperidone

Triethylamine (0.7 ml) and a solution in anhydrous methylene chloride (10 ml) of (E)-4-chlorostyrylsulfonyl chloride (1.1 g) prepared by a documented (WO96/10022) method were added to a solution of 4-piperidone monohydrate hydrochloride (0.5 g) in anhydrous methylene chloride (50 ml) and the mixture was stirred overnight in an argon atmosphere at room temperature. Water was added to the reaction mixture and was extracted with methylene chloride. It was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride) to give the titled compound (500 mg). NMR spectrum (*DMSO-d_6) δ ppm: 7.83~7.77 (2H, m), 7.55~7.38 (4H, m), 3.49 (4H, t, J=6Hz), 2.47 (4H, t, J=6Hz)

[0128]

<Step 2> Synthesis of 1-[1-((E)-4-chlorostyrylsulfonyl)piperidin-4-yl]-4-(4-pyridyl)piperazine

Acetic acid (0.18 ml) was added to a solution in anhydrous methylene chloride (12 ml) of a portion (490 mg) of the compound obtained in step 1 and 1-(4-pyridyl)piperazine (254 mg) prepared by a documented (Japanese Patent Application Laid-Opened No. 192225/1994) method and the mixture was stirred for 30 minutes in an argon atmosphere at room temperature. To the stirred mixture, sodium triacetoxyborohydride (660 mg) was added and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, which was rendered alkaline with 1 N sodium hydroxide solution and was extracted with methylene chloride. It was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 19:1 - 9:1) to give the titled compound (290 mg).

[0129]

HRMS: $C_{22}H_{27}ClN_4O_2S(M^+)$ Cal'd 446.1543 Found 446.1555

NMR spectrum (*DMSO-d_6) δ ppm: 8.20~8.10 (2H, m), 7.81 (2H, d, J=9Hz), 7.52 (2H, d, J=9Hz), 7.46~

7.30 (2H, m), 6.90～6.75 (2H, m), 3.65～3.55 (2H, m), 3.43～3.18 (4H, m), 2.75～2.62 (2H, m), 2.61～2.44 (4H, m), 2.44～2.31 (1H, m), 1.90～1.80 (2H, m), 1.58～1.40 (2H, m)

[0130]

Example 2 Synthesis of 1-[1-((E)-4-chlorostyrylsulfonyl)piperidin-4-ylmethyl]-4-(4-pyridyl)piperazine

<Step 1> Synthesis of 1-[(E)-4-chlorostyrylsulfonyl)]piperidin-4-yl methanol

Triethylamine (0.88 ml) and (E)-4-chlorostyrylsulfonyl chloride (1.03 g) were added to a solution in anhydrous methylene chloride (10 ml) of piperidin-4-yl methanol (0.5 g) prepared by a documented (J. Med. Chem., 34, 1073, 1991) method and the mixture was stirred for 4 hours in an argon atmosphere at room temperature. Water was added to the reaction mixture, which was then was extracted with methylene chloride. It was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 99:1 - 97:3) to give the titled compound (180 mg).

[0131]

NMR spectrum (*DMSO-d_6) δ ppm: 7.80 (2H, d, J=9Hz), 7.52 (2H, d, J=9Hz), 7.38 (1H, d, J=16Hz), 7.33 (1H, d, J=16Hz), 4.54 (1H, t, J=5Hz), 3.63~3.50 (2H, m), 3.28~3.21 (2H, m), 2.70~2.56 (2H, m), 1.80~1.35 (3H, m), 1.23~1.07 (2H, m)

[0132]

<Step 2> Synthesis of 1-[1-((E)-4-chlorostyrylsulfonyl)piperidin-4-ylmethyl]-4-(4-pyridyl)piperazine

A solution of oxalyl chloride (0.05 ml) in anhydrous methylene chloride (1.33 ml) was cooled to -78°C in an argon atmosphere. To the cooled solution, a solution of anhydrous dimethyl sulfoxide (0.09 ml) in anhydrous methylene chloride (1.33 ml) was added dropwise over 20 minutes. Then, a solution in anhydrous methylene chloride (1.33 ml) of a portion (150 mg) of the compound obtained in step 1 was added dropwise over 20 minutes. After stirring for 1 hour at between -65°C and -60°C, the mixture was cooled to -78°C and triethylamine (0.25 ml) was added. It was stood at room temperature, water was added and extraction with methylene chloride was conducted. It was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The resulting residue was

suspended in anhydrous methylene chloride (2.0 ml) and 1-(4-pyridyl)piperazine (42 mg) and acetic acid (0.02 ml) were added in that order. It was stirred at room temperature for 30 minutes in an argon atmosphere, sodium triacetoxyborohydride (0.10 g) was added and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, which was adjusted to pH 9 with 1 N sodium hydroxide solution and was extracted with methylene chloride. It was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 19:1) to yield the titled compound (60 mg).

[0133]

NMR spectrum (*DMSO-d_6) δ ppm: 8.17~8.11 (2H, m), 7.81 (2H, d, J=9Hz), 7.52 (2H, d, J=9Hz), 7.44~7.29 (2H, m), 6.83~6.77 (2H, m), 3.63~3.52 (2H, m), 3.31~3.20 (4H, m), 2.72~2.58 (2H, m), 2.47~2.37 (4H, m), 2.17 (2H, d, J=7Hz), 1.86~1.75 (2H, m), 1.70~1.55 (1H, m), 1.25~1.05 (2H, m)

[0134]

Example 3 Synthesis of 1-[(E)-4-chlorostyrylsulfonyl]-4-[1-(4-pyridyl)piperidin-4-

ylmethyl]piperazine

<Step 1> Synthesis of 4-[1-(4-pyridyl)piperidine]carbaldehyde

A solution of oxalyl chloride (1.77 ml) in anhydrous methylene chloride (85 ml) was cooled to -78°C in an argon atmosphere. To the cooled solution, a solution of anhydrous dimethyl sulfoxide (3.25 ml) in anhydrous methylene chloride (85 ml) was added dropwise over 20 minutes. Then, a solution in anhydrous methylene chloride (48 ml) and anhydrous dimethyl sulfoxide (48 ml) of 1-(4-pyridyl)piperidin-4-yl methanol (3.0 g) prepared by a documented (EP 0359389) method was added dropwise over 20 minutes. After stirring at between -65°C and -60°C for 1 hour, the mixture was cooled to -78°C and triethylamine (8.31 ml) was added. It was stood at room temperature, water was added and extraction with methylene chloride was conducted. It was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The resulting aldehyde was rather labile and should preferably be used in the next reaction without being purified. It can, however, be analyzed with reasonable accuracy. The above-described treatment was done quickly and the concentrated residue was dissolved in $CDCl_3$ and subjected

to NMR measurement; a signal for the proton of aldehyde was identified but disappeared with time.

[0135]

EIMS: 190 (M^+)

NMR spectrum (*$CDCl_3$) δ ppm: 9.56 (1H, s), 8.16~7.99 (2H, m), 6.82~6.69 (2H, m), 3.83~3.71 (2H, m),
3.02~2.90 (2H, m), 2.61~2.45 (1H, m), 1.90~1.78 (2H, m), 1.52~1.36 (2H, m)

[0136]

<Step 2> Synthesis of 1-t-butoxycarbonyl-4-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazine

The product of step 1 was suspended in anhydrous methylene chloride (65 ml); to the suspension, 1-t-butoxycarbonyl piperazine (3.19 g) and acetic acid (1.55 ml) were added in that order. After stirring at room temperature for 30 minutes in an argon atmosphere, sodium triacetoxyborohydride (6.61 g) was added and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, which was adjusted to pH 9 with 1 N sodium hydroxide solution and was extracted with methylene chloride. It was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The

residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 99:1) to give the titled compound (0.59 g).

[0137]

HRMS: $C_{20}H_{32}N_4O_2$ (M^+) Cal'd 360.2525 Found 360.2545

NMR spectrum (*$CDCl_3$) δ ppm: 8.26~8.20 (2H, m), 6.68~6.62 (2H, m), 3.92~3.82 (2H, m), 3.46~3.37 (4H, m), 2.90~2.77 (2H, m), 2.40~2.31 (4H, m), 2.20 (2H, d, J=7Hz), 1.90~1.68 (3H, m), 1.46 (9H, s), 1.30~1.18 (2H, m)

[0138]

<Step 3> Synthesis of 1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazine trifluoroacetate

Anisole (2.23 ml) and ice water-cooled trifluoroacetic acid (17.2 ml) were added to the compound (3.21 g) obtained in step 2 and the mixture was stirred overnight at room temperature in an argon atmosphere. Ether (200 ml) was added to the reaction mixture and stirred vigorously. After standing, the supernatant was removed by decantation and another 200-ml portion of ether was added; this procedure was repeated. Ether (200 ml) was added to the residue and the mixture was divided into adequately fine particles, which were filtered to give the titled compound (3.24 g).

[0139]

HRMS: $C_{15}H_{24}N_4$ (M^+) Cal'd 260.2001 Found 260.2003

NMR spectrum (*DMSO-d_6) δ ppm: 8.30~8.18 (2H, m), 7.25~7.17 (2H, m), 4.29~4.18 (2H, m), 4.00~3.35 (4H, m), 3.35~3.09 (6H, m), 2.50~2.40 (2H, m), 2.12~1.98 (1H, m), 1.93~1.82 (2H, m), 1.23~1.06 (2H, m)

[0140]

<Step 4> Synthesis of 1-[(E)-4-chlorostyrylsulfonyl]-4-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazine

Triethylamine (0.091 ml) and (E)-4-chlorostyrylsulfonyl chloride (15.6 mg) were added to a suspension in anhydrous methylene chloride (1.0 ml) of a portion (47 mg) of the compound obtained in step 3. The resulting mixture was stirred overnight at room temperature in an argon atmosphere. Water was added to the reaction mixture, rendered alkaline with 1 N sodium hydroxide and was extracted with methylene chloride. It was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 19:1 - 9:1) to yield the titled compound (13 mg).

[0141]

HRMS: $C_{23}H_{29}ClN_4O_2S$ (M^+) Cal'd 460.1699 Found 460.1709

NMR spectrum (*CDCl3) δ ppm: 8.26～8.17 (2H, m), 7.47～7.37 (5H, m), 6.73～6.62 (3H, m), 3.93～3.80 (2H, m), 3.30～3.16 (4H, m), 112.89～2.75 (2H, m), 2.60～2.47 (

4H, m), 2.24 (2H, d, J=7Hz), 1.89～1.65 (3H, m), 1.30～1.13 (2H, m)

[0142]

In subsequent Examples 4 - 22, a commercial grade of sulfonyl chloride or sulfonyl chloride obtained by chlorinating a commercial grade of sulfonic acid was used and the method of <step 4> in Example 3 was repeated to synthesize the end compounds. The property data for each compound are given in Table 1.

[0143]

[Table 1]

TABLE 1-1

Ex. No.	NMR (ppm) (* : 300MHz, Without asterisk : 270MHz)
12	CDCl3:8.23-8.15(2H,m),7.90-7.76(2H,m),7.56-7.45(2H,m),6.67-6.60(2H,m),4.33(2H,s),4.18(2H,q,J=7Hz),3.90-3.80(2H,m),3.32-3.20(4H,m),2.90-2.76(2H,m),2.57-2.45(4H,m),2.20(2H,d,J=7Hz),1.85-1.62(3H,m),1.30-1.10(2H,m),1.26(3H,t,J=7Hz)
13	CDCl3*:8.25-8.17(2H,m),8.14-8.07(1H,m),7.93-7.86(1H,m),7.62-7.53(2H,m),6.71-6.63(2H,m),3.95-3.84(2H,m),3.47-3.35(4H,m),2.94-2.80(2H,m),2.60-2.49(4H,m),2.24(2H,d,J=7Hz),1.91-1.67(3H,m),1.35-1.12(2H,m)
14	CDCl3:8.48-8.40(1H,m),8.38-8.17(2H,m),7.60-7.22(3H,m),6.74-6.64(2H,m),4.00-3.85(2H,m),3.60-3.44(4H,m),2.98-2.82(2H,m),2.75-2.61(4H,m),2.31(2H,d,J=7Hz),1.97-1.50(3H,m),1.40-1.16(2H,m)
15	CDCl3:8.25-8.14(2H,m),7.75-7.66(1H,m),7.61-7.33(4H,m),6.77-6.66(2H,m),4.00-3.88(2H,m),3.38-3.23(4H,m),3.05-2.90(2H,m),2.59-2.42(4H,m),2.22(2H,d,J=7Hz),1.93-1.71(3H,m),1.31-1.10(2H,m)
16	CDCl3:8.21-8.16(2H,m),7.68(1H,d,J=2Hz),7.51(1H,d,J=9Hz),7.44(1H,dd,J=2,9Hz),7.31(1H,s),6.69-6.62(2H,m),3.95-3.85(2H,m),3.35-3.25(4H,m),2.93-2.80(2H,m),2.55-2.47(4H,m),2.22(2H,d,J=7Hz),1.90-1.60(3H,m),1.35-1.10(2H,m)
17	CDCl3:8.31-8.13(3H,m),8.07(1H,d,J=9Hz),7.82(1H,dd,J=2,9Hz),6.66-6.53(2H,m),3.88-3.71(2H,m),3.14-2.96(4H,m),2.92(3H,s),2.85-2.68(2H,m),2.61-2.39(4H,m),2.19(2H,d,J=7Hz),1.90-1.55(3H,m),1.31-1.03(2H,m)
18	CDCl3:8.25-8.18(2H,m),7.83(2H,d,J=9Hz),7.74(2H,d,J=9Hz),7.66-7.58(2H,m),7.56-7.40(3H,m),6.65-6.57(2H,m),3.88-3.76(2H,m),3.16-3.02(4H,m),2.86-2.71(2H,m),2.60-2.47(4H,m),2.21(2H,d,J=7Hz),1.85-1.59(3H,m),1.30-1.08(2H,m)
19	CDCl3+MeOH-d4:8.64-8.55(1H,m),8.36-7.97(3H,m),7.47(1H,d,J=8Hz),6.85-6.59(2H,m),4.03-3.86(2H,m),3.38-3.13(4H,m),3.07-2.87(2H,m),2.58-2.06(6H,m),1.94-1.68(3H,m),1.37-1.07(2H,m)
20	CDCl3:8.25-8.18(2H,m),7.87-7.85(1H,m),7.55-7.44(2H,m),6.70-6.65(2H,m),3.98-3.86(2H,m),3.67(2H,s),3.25-3.16(4H,m),3.03-2.90(2H,m),2.50-2.41(4H,m),2.20-2.15(2H,m),2.05-1.80(3H,m),1.30-1.10(2H,m)

[0144]

[Table 2]

TABLE 1-2

Ex. No.	NMR (ppm) (* : 300MHz, Without asterisk : 270MHz)
4	$CDCl_3$:8.36-8.32(1H,m),8.20-8.11(2H,m),8.04-7.92(3H,m),7.76(1H,dd,J=2,9Hz),7.72-7.60(2H,m),6.69-6.62(2H,m),3.93-3.82(2H,m),3.16-3.04(4H,m),2.98-2.78(2H,m),2.55-2.44(4H,m),2.19(2H,d,J=7Hz),1.86-1.63(3H,m),1.29-1.04(2H,m)
5	$CDCl_3$:8.32-8.29(1H,m),8.22-8.16(2H,m),8.01-7.86(3H,m),7.77(1H,dd,J=2,9Hz),7.58(1H,dd,J=2,9Hz),6.73-6.65(2H,m),3.97-3.84(2H,m),3.16-2.88(6H,m),2.56-2.43(4H,m),2.19(2H,d,J=7Hz),1.90-1.67(3H,m),1.25-1.06(2H,m)
6	$CDCl_3$:8.32-8.28(1H,m),8.23-8.18(2H,m),8.11(1H,d,J=2Hz),7.90(1H,d,J=9Hz),7.85(1H,d,J=9Hz),7.78(1H,dd,J=2,9Hz),7.71(1H,dd,J=2,9Hz),6.62-6.57(2H,m),3.88-3.74(2H,m),3.18-2.99(4H,m),2.88-2.70(2H,m),2.59-2.42(4H,m),2.18(2H,d,J=7Hz),1.81-1.57(3H,m),1.35-1.04(2H,m)
7	$CDCl_3$*:8.22-8.16(2H,m),7.95-7.86(2H,m),7.80(1H,s),7.56-7.46(2H,m),6.75-6.68(2H,m),4.00-3.92(2H,m),3.25-3.13(4H,m),3.06-2.95(2H,m),2.60-2.50(4H,m),2.23(2H,d,J=7Hz),1.93-1.72(3H,m),1.28-1.10(2H,m)
8	DMSO-d_6:8.21(1H,dd,J=5,8Hz),8.14-8.08(2H,m),8.04(1H,s),7.94-7.87(1H,m),7.51(1H,dt,J=3,9Hz),6.91-6.83(2H,m),4.03-3.87(2H,m),3.14-2.97(4H,m),2.95-2.78(2H,m),2.57-2.49(4H,m),2.15(2H,d,J=7Hz),1.85-1.62(3H,m),1.12-0.93(2H,m)
9	$CDCl_3$*:8.25-8.17(2H,m),7.90-7.80(2H,m),7.76(1H,s),7.48-7.42(1H,m),6.67-6.59(2H,m),3.90-3.78(2H,m),3.23-3.11(4H,m),2.85-2.74(2H,m),2.60-2.48(4H,m),2.21(2H,d,J=7Hz),1.85-1.53(3H,m),1.30-1.09(2H,m)
10	$CDCl_3$*:8.24-8.11(2H,m),7.95(1H,s),7.49-7.36(2H,m),6.87-6.66(3H,m),4.06-3.90(5H,m),3.25-2.95(6H,m),2.61-2.40(4H,m),2.22(2H,d,J=7Hz),1.95-1.72(3H,m),1.33-1.07(2H,m)
11	$CDCl_3$*:8.24-8.18(2H,m),7.77(1H,d,J=9Hz),7.71(1H,s),7.29(1H,d,J=2Hz),7.09(1H,dd,J=2,9Hz),6.65-6.59(2H,m),3.91(3H,s),3.89-3.78(2H,m),3.24-3.06(4H,m),2.85-2.72(2H,m),2.58-2.44(4H,m),2.21(2H,d,J=7Hz),1.85-1.56(3H,m),1.35-1.08(2H,m)

[0145]

[Table 3]

TABLE 1-3

Ex. No.	NMR (ppm) (* : 300MHz, Without asterisk : 270MHz)
21	$CDCl_3$:8.31(1H,s),8.20-8.10(2H,m),8.03(1H,d,J=9Hz), 7.95-7.82(2H,m),7.78-7.70(1H,m),7.68-7.58(1H,m),6.62-6.57(2H,m),3.89-3.78(2H,m),3.15-2.98(4H,m),2.88-2.73 (2H,m),2.56-2.44(4H,m),2.37(3H,s),2.18(2H,d,J=7Hz), 1.80-1.60(3H,m),1.28-1.05(2H,m)
22	$CDCl_3$*:8.28-8.13(3H,m),7.96(1H,d,J=9Hz),7.73-7.64(1H, m),7.47-7.37(2H,m),6.96-6.90(1H,m),6.63-6.54(2H,m), 4.40-4.10(1H,m),3.90-3.74(2H,m),3.16-2.97(4H,m),2.83-2.68(2H,m),2.58-2.40(4H,m),2.17(2H,d,J=7Hz),1.80-1.60 (3H,m),1.22-1.02(2H,m)

[0146]

Example 23 Synthesis of 4-[(E)-4-chlorostyrylsulfonyl]-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

<Step 1> Synthesis of 4-[N-(2-(t-butoxycarbonylamino)ethyl)aminomethyl]-1-(4-pyridyl)piperidine borane complex

A crude product obtained from 1-(4-pyridyl)piperidin-4-yl methanol (3.0 g) by the method of <step 1> in Example 3 was suspended in anhydrous methylene chloride (13 ml). To the suspension, N-t-butoxycarbonyl-1,2-ethylenediamine (0.54 g) and acetic acid (0.31 ml) were added in that order. After stirring at room temperature for 30 minutes in an

argon atmosphere, sodium triacetoxyborohydride (1.33 g) was added and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, adjusted to pH 9 with 1 N sodium hydroxide solution, and was extracted with methylene chloride. It was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 99:1) to give the titled compound (0.62 g).

[0147]

NMR spectrum ($CDCl_3$) δ ppm: 8.22~8.14 (2H, m), 6.73~6.64 (2H, m), 4.20~3.92 (2H, m), 3.29~3.12 (2H, m), 3.12~2.98 (2H, m), 2.73 (2H, t, J=6Hz), 2.54 (2H, d, J=7Hz), 1.99~1.72 (3H, m), 1.45 (9H, s), 1.33~1.15 (2H, m)

[0148]

<Step 2> Synthesis of 4-[N-bromoacetyl-N-[2-(t-butoxycarbonylamino)ethyl]aminomethyl]-1-(4-pyridyl)piperidine borane complex

Triethylamine (0.28 ml) was added to a solution in anhydrous methylene chloride (5 ml) of a portion (0.6 g) of the compound obtained in step 1. To the mixture, a solution of bromoacetyl chloride (0.31 g) in anhydrous

methylene chloride (5 ml) was added dropwise under cooling with ice water and the mixture was stirred at room temperature for 2 hours in an argon atmosphere. Ice water was added to the reaction mixture and extraction with methylene chloride was conducted. It was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 99:1) to give the titled compound (0.61 g).

[0149]

NMR spectrum (*$CDCl_3$) δ ppm: 8.26～8.15 (2H, m), 6.75～6.65 (2H, m), 4.18～3.84 (4H, m), 3.56～3.45 (2H, m), 3.37～3.21 (4H, m), 3.13～2.99 (2H, m), 2.25～2.10 (1H, m), 1.92～1.77 (2H, m), 1.44 (9H, s), 1.39～1.19 (2H, m)

[0150]

<Step 3> Synthesis of 4-[N-(2-aminoethyl)-N-bromoacetylaminomethyl]-1-(4-pyridyl)piperidine trifluoroacetate

To a portion (0.54 g) of the compound obtained in step 2, anisole (0.29 g) and ice water-cooled trifluoroacetic acid (2.3 ml) were added and the mixture was stirred at room temperature for 1.5 hours in an argon atmosphere.

Ether (50 ml) was added to the reaction mixture and stirred vigorously. After standing, the supernatant was removed by decantation and another 50 ml of ether was added; this procedure was repeated. Ether (50 ml) was added to the residue and the mixture was divided into adequately fine particles, which were filtered to give the titled compound (0.58 g).

[0151]

NMR spectrum (*DMSO-d_6) δ ppm: 8.26~8.16 (2H, m), 7.23-7.13 (2H, m), 4.55-4.35 (2H, m), 4.34~4.18 (2H, m), 3.60~3.45 (2H, m), 3.29~2.87 (6H, m), 2.15~1.96 (1H, m), 1.78~1.63 (2H, m), 1.32~1.04 (2H, m)

[0152]

<Step 4> Synthesis of 1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

To a solution in anhydrous dimethylformamide (20 ml) of a portion (0.46 g) of the compound obtained in step 3, triethylamine (1.43 ml) was added under cooling with ice water; the mixture was stirred at the same temperature for 1 hour, then at room temperature for another one hour. The solvent was evaporated under reduced pressure and the residue was used as such in the next reaction.

[0153]

HRMS: $C_{15}H_{22}N_4O$ (M^+) Cal'd 274.1793 Found 274.1767

NMR spectrum (*$CDCl_3$) δ ppm: 8.24~8.20 (2H, m), 6.67~6.63 (2H, m), 3.96~3.86 (2H, m), 3.55 (2H, s), 3.40~3.26 (4H, m), 3.14~3.06 (2H, m), 2.92~2.81 (2H, m), 2.10~1.94 (1H, m), 1.90~1.72 (2H, m), 1.42~1.24 (2H, m)

[0154]

<Step 5> Synthesis of 4-[(E)-4-chlorostyrylsulfonyl]-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

The crude product of step 4 was suspended in anhydrous methylene chloride (34 ml); to the suspension, triethylamine (0.72 ml) and a solution of (E)-4-chlorostyrylsulfonyl chloride (245 mg) in anhydrous methylene chloride (5 ml) were added in that order, and the mixture was stirred overnight at room temperature in an argon atmosphere. Water was added to the reaction mixture, which was adjusted to pH 9 with 1 N sodium hydroxide solution and was extracted with methylene chloride. It was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 99:1 - 95:5) to yield the titled compound (130 mg).

[0155]

HRMS: $C_{23}H_{27}ClN_4O_3S$ (M^+) Cal'd 474.1492 Found 474.1503

NMR spectrum (*$CDCl_3$) δ ppm: 8.28～8.20 (2H, m), 7.49 (1H, d, J=16Hz), 7.48～7.38 (4H, m), 6.69～6.58 (3H, m), 3.89 (2H, s), 3.94～3.78 (2H, m), 3.57～3.44 (4H, m), 3.32 (2H, d, J=7Hz), 2.88～2.72 (2H, m), 2.05～1.87 (1H, m), 1.83～1.64 (2H, m), 1.40～1.22 (2H, m)

[0156]

Example 24 Synthesis of 4-(6-bromonaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

Using 6-bromonaphthalen-2-ylsulfonyl chloride (22.3 mg), synthesis was performed by the method of <step 5> in Example 23 to yield the titled compound (12 mg).

[0157]

HRMS: $C_{25}H_{27}BrN_4O_3S$ (M^+) Cal'd 542.0987 Found 542.1022

NMR spectrum (*$CDCl_3$) δ ppm: 8.37～8.34 (1H, m), 8.26～8.19 (2H, m), 8.16～8.11 (1H, m), 7.93 (1H, d, J=9Hz), 7.88 (1H, d, J=9Hz), 7.80 (1H, dd, J=2, 9Hz), 7.75 (1H, dd, J=2, 9Hz), 6.66～6.59 (2H, m), 3.89～3.77 (2H, m), 3.80 (2H, s), 3.49～3.38 (4H, m), 3.25 (2H, d, J=7Hz), 2.84～2.72 (2H, m), 1.99～1.83 (1H, m), 1.68～1.57 (2H, m), 1.35～1.17 (2H, m)

[0158]

Example 401 Synthesis of 1-[(E)-4-chlorostyrylsulfonyl]-4-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazine methanesulfonate

Methanesulfonic acid (10.4 mg) was added to a solution in methanol (1 ml) of the compound (50 mg) obtained in <step 4> of Example 3. The solvent was evaporated under reduced pressure to yield the titled compound (60 mg).

[0159]

NMR spectrum (*DMSO-d_6) δ ppm: 8.22~8.14 (2H, m), 7.83 (2H, d, J=8Hz), 7.53 (2H, d, J=8Hz), 7.47~7.33 (2H, m), 7.19~7.12 (2H, m), 4.24~4.12 (2H, m), 3.55~3.25 (4H, m), 3.21~3.04 (6H, m), 2.33 (3H, s), 2.30~2.18 (2H, m), 2.10~1.78 (3H, m), 1.18~1.00 (2H, m)

[0160]

Example 402 Synthesis of 4-[(E)-4-chlorostyrylsulfonyl]-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one methanesulfonate

Methanesulfonic acid (8.49 mg) was added to a solution in methanol (1 ml) of the compound (42 mg) obtained in <step 5> of Example 23. The solvent was evaporated under reduced pressure to yield the titled compound (50 mg).

[0161]

NMR spectrum (*DMSO-d_6) δ ppm: 8.22~8.13 (2H, m),

7. 84～7. 77 (2H, m), 7. 57～7. 38 (4H, m), 7. 16～7. 08 (2H, m), 4. 18～4. 06 (2H, m), 3. 77 (2H, s), 3. 55～3. 27 (2H, m), 3. 25～2. 99 (4H, m), 2. 56～2. 43 (2H, m), 2. 29 (3H, s), 2. 01～1. 95 (1H, m), 1. 72～1. 61 (2H, m), 1. 19～1. 03 (2H, m)

[0162]

The structures of the compounds in the Examples 1 to 402 of the present invention are shown in Fig. 1. The Examples 25 to 400 are only shown in Figs.

[0163]

[Effects of the Invention]

The compounds of the present invention are a specific FXa inhibitor and have a potent anticoagulation effect. They are,
therefore, useful as anticoagulants or as preventive or therapeutic agents for diseases caused by thrombus or embolus. Examples of such diseases include diseases from ischemic cerebrovascular disorders such as cerebral thrombosis, cerebral infarction, cerebral embolism and transient cerebral ischemic attacks (TIA), diseases associated with ischemic heart diseases such as acute or chronic myocardial infarction, unstable angina pectoris and coronary thrombolysis, diseases from pulmonary infarction, pulmonary embolism and other conditions of pulmonary angiopathy, and diseases from various cases of angiopathy

including peripheral arterial obstruction, deep venous thrombosis, disseminated intravascular coagulation (DIC), thrombosis after artificial blood vessel or heart valve replacement, reocclusion and restenosis following coronary artery bypass surgery, reocclusion and restenosis on or after PTCA, and thrombosis on extracorporeal circulation of blood, and the like. The compounds of the present invention are also useful as preventive or therapeutic agent for infections with influenza virus.

[BRIEF DESCRIPTION OF THE DRAWINGS]

[FIG. 1] Figs. 1 - 34 tabulate the structural formulae of the compounds in the Examples of the present invention (Fig. 1); shown in the column S_1 are exemplary 6-membered rings together with the substituent R_1; shown in the column S2 are exemplary structures of the bridge which, either directly or via an alkylene group, connects two rings comprising combinations of piperazine or piperidine rings; shown in the column S_3 are examples of the formula -Z_1-Z_2-Q.

[FIG. 2] The structural formulae of the compounds of the present invention are shown.

[FIG. 3] The structural formulae of the compounds of the present invention are shown.

[FIG. 4] The structural formulae of the compounds of

the present invention are shown.

[FIG. 5] The structural formulae of the compounds of the present invention are shown.

[FIG. 6] The structural formulae of the compounds of the present invention are shown.

[FIG. 7] The structural formulae of the compounds of the present invention are shown.

[FIG. 8] The structural formulae of the compounds of the present invention are shown.

[FIG. 9] The structural formulae of the compounds of the present invention are shown.

[FIG. 10] The structural formulae of the compounds of the present invention are shown.

[FIG. 11] The structural formulae of the compounds of the present invention are shown.

[FIG. 12] The structural formulae of the compounds of the present invention are shown.

[FIG. 13] The structural formulae of the compounds of the present invention are shown.

[FIG. 14] The structural formulae of the compounds of the present invention are shown.

[FIG. 15] The structural formulae of the compounds of the present invention are shown.

[FIG. 16] The structural formulae of the compounds of

the present invention are shown.

[FIG. 17] The structural formulae of the compounds of the present invention are shown.

[FIG. 18] The structural formulae of the compounds of the present invention are shown.

[FIG. 19] The structural formulae of the compounds of the present invention are shown.

[FIG. 20] The structural formulae of the compounds of the present invention are shown.

[FIG. 21] The structural formulae of the compounds of the present invention are shown.

[FIG. 22] The structural formulae of the compounds of the present invention are shown.

[FIG. 23] The structural formulae of the compounds of the present invention are shown.

[FIG. 24] The structural formulae of the compounds of the present invention are shown.

[FIG. 25] The structural formulae of the compounds of the present invention are shown.

[FIG. 26] The structural formulae of the compounds of the present invention are shown.

[FIG. 27] The structural formulae of the compounds of the present invention are shown.

[FIG. 28] The structural formulae of the compounds of

the present invention are shown.

[FIG. 29] The structural formulae of the compounds of the present invention are shown.

[FIG. 30] The structural formulae of the compounds of the present invention are shown.

[FIG. 31] The structural formulae of the compounds of the present invention are shown.

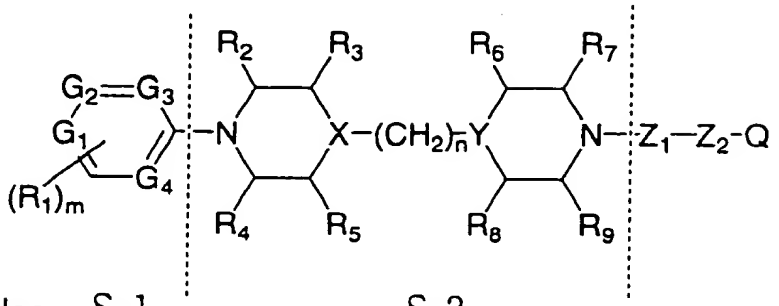
[FIG. 32] The structural formulae of the compounds of the present invention are shown.

[FIG. 33] The structural formulae of the compounds of the present invention are shown.

[FIG. 34] The structural formulae of the compounds of the present invention are shown.

【TYPE OF THE DOCUMENT】Drawings

【FIG.1】



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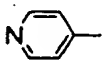
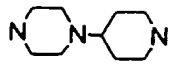
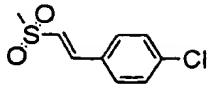
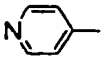
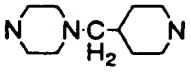
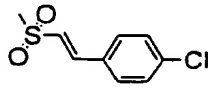
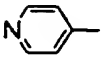
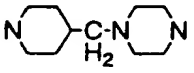
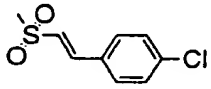
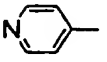
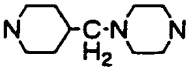
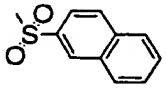
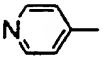
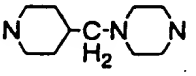
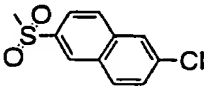
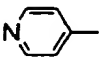
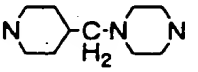
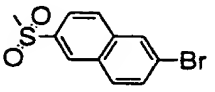
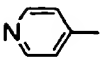
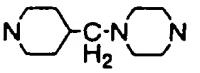
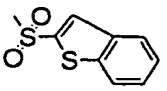
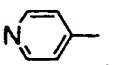
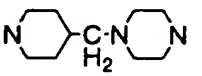
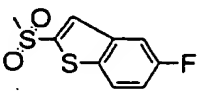
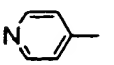
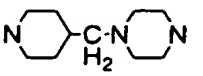
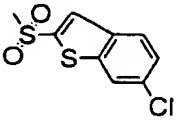
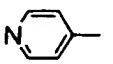
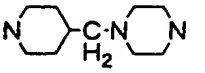
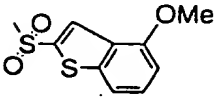
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

【FIG.2】

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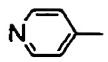
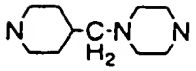
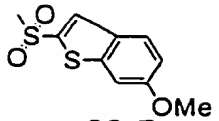
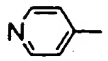
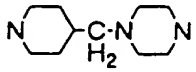
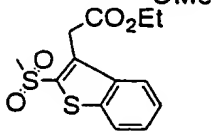
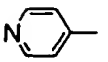
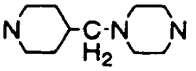
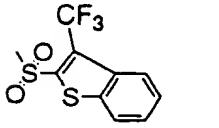
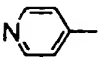
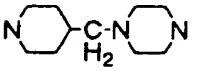
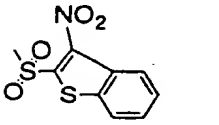
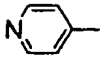
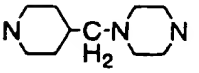
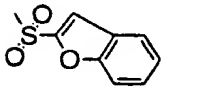
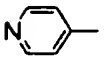
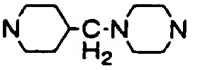
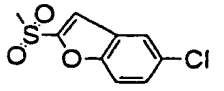
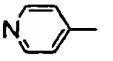
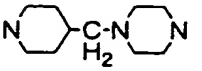
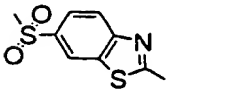
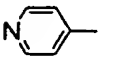
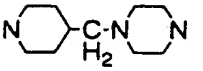
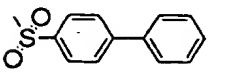
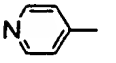
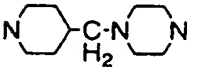
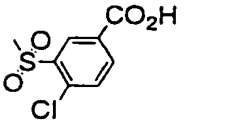
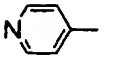
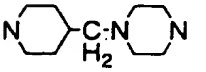
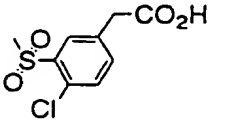
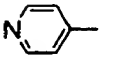
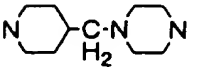
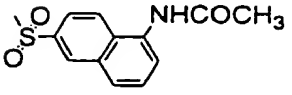
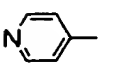
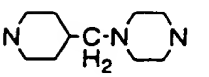
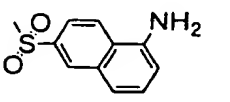
1 1			
1 2			
1 3			
1 4			
1 5			
1 6			
1 7			
1 8			
1 9			
2 0			
2 1			
2 2			

【FIG.3】

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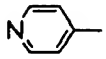
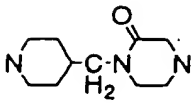
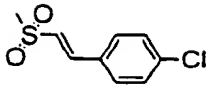
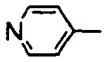
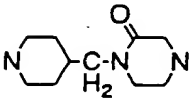
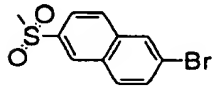
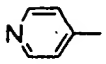
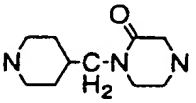
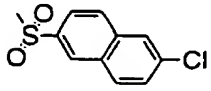
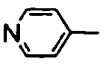
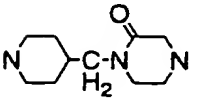
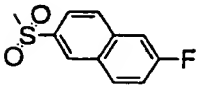
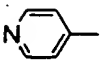
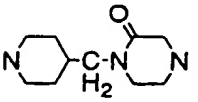
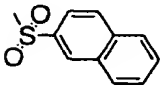
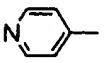
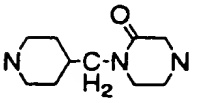
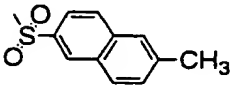
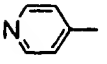
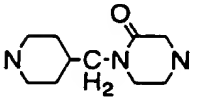
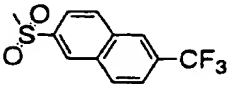
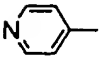
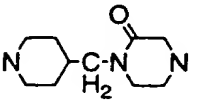
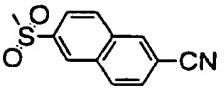
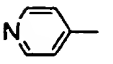
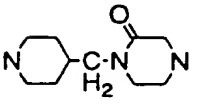
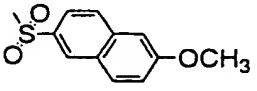
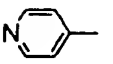
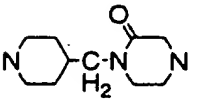
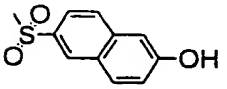
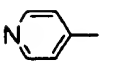
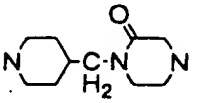
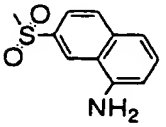
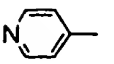
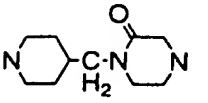
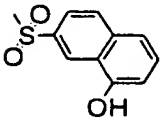
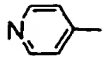
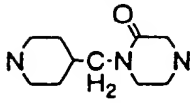
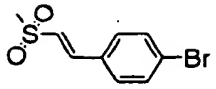
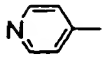
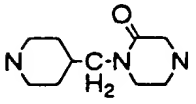
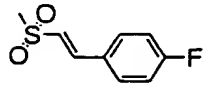
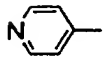
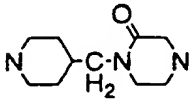
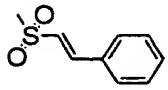
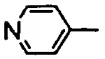
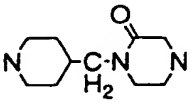
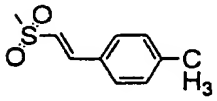
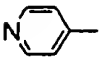
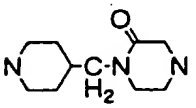
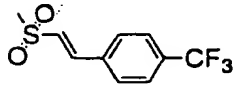
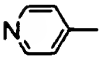
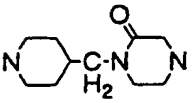
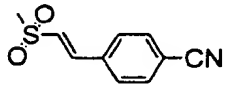
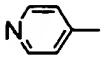
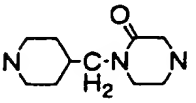
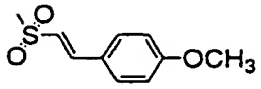
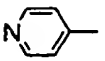
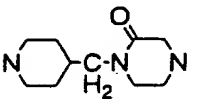
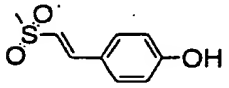
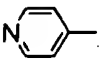
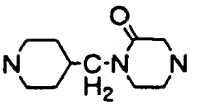
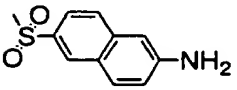
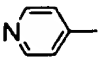
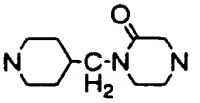
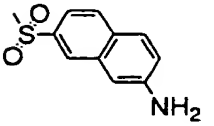
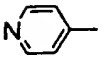
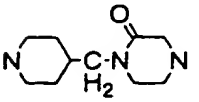
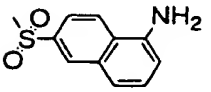
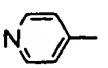
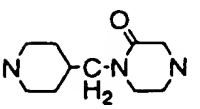
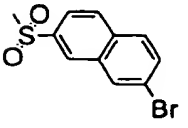
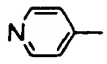
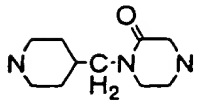
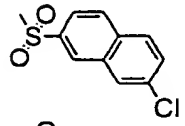
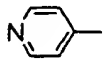
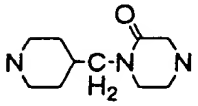
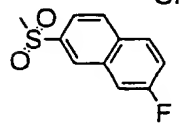
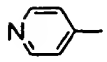
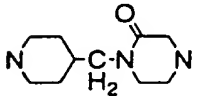
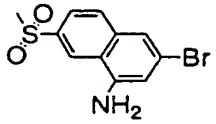
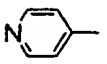
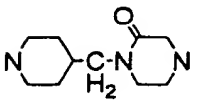
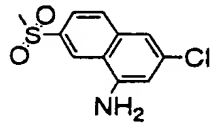
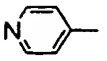
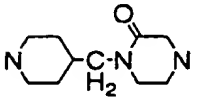
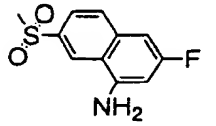
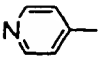
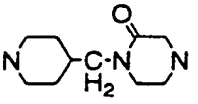
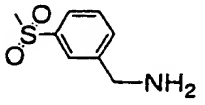
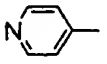
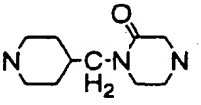
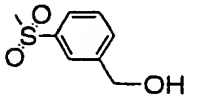
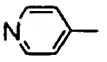
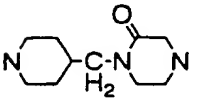
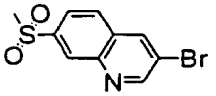
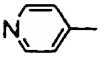
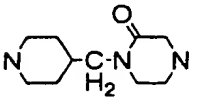
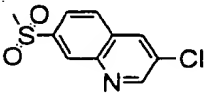
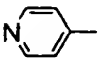
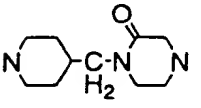
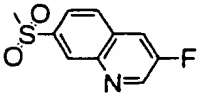
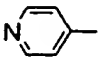
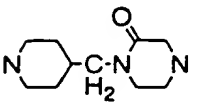
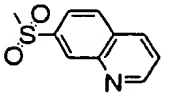
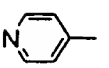
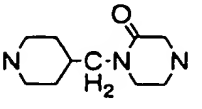
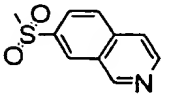
2 3			
2 4			
2 5			
2 6			
2 7			
2 8			
2 9			
3 0			
3 1			
3 2			
3 3			
3 4			

【FIG.4】

	S 1	S 2	S 3
3 5			
3 6			
3 7			
3 8			
3 9			
4 0			
4 1			
4 2			
4 3			
4 4			
4 5			
4 6			

【FIG.5】

	S 1	S 2	S 3
4 7			
4 8			
4 9			
5 0			
5 1			
5 2			
5 3			
5 4			
5 5			
5 6			
5 7			
5 8			

【FIG.6】

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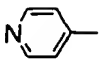
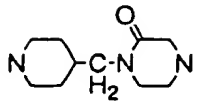
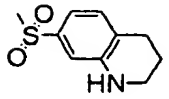
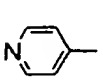
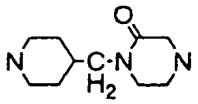
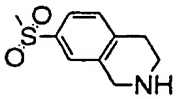
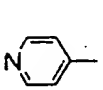
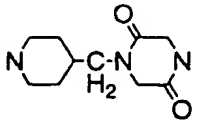
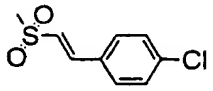
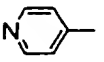
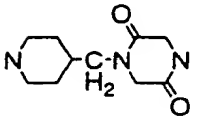
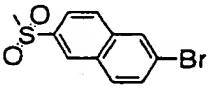
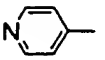
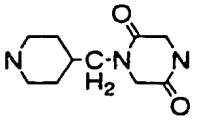
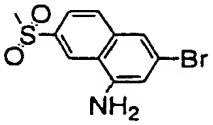
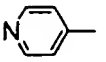
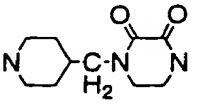
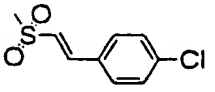
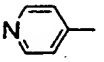
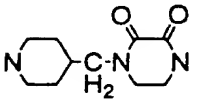
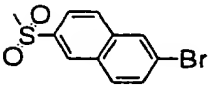
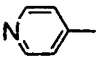
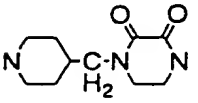
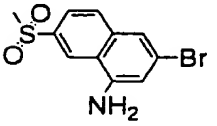
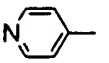
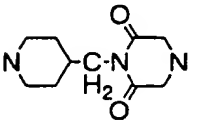
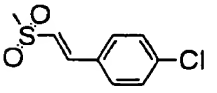
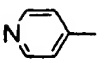
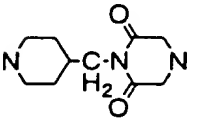
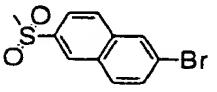
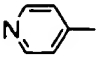
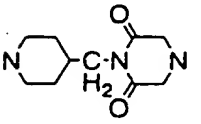
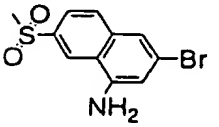
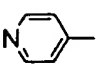
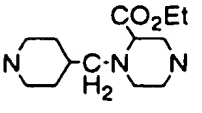
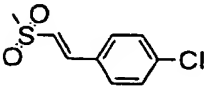
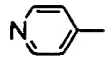
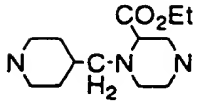
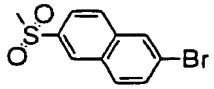
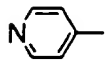
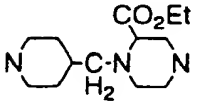
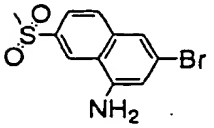
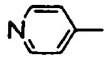
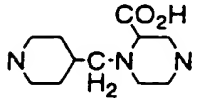
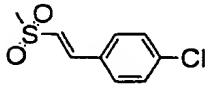
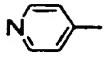
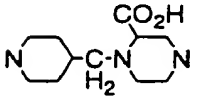
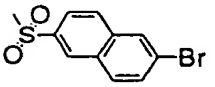
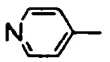
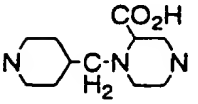
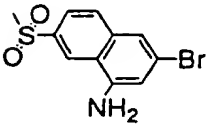
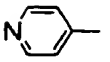
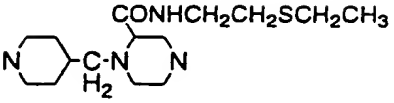
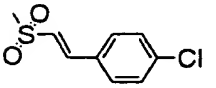
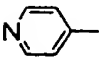
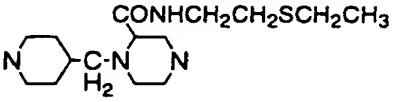
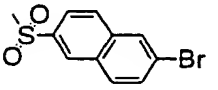
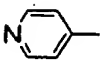
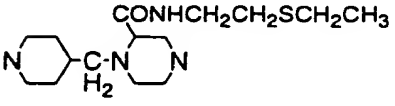
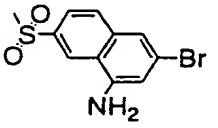
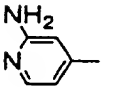
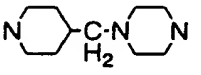
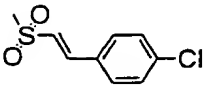
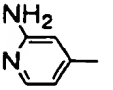
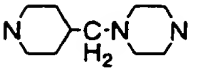
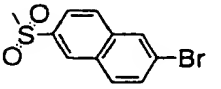
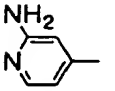
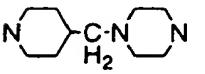
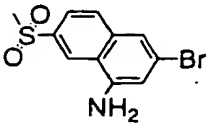
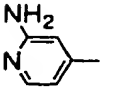
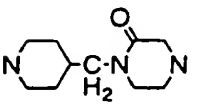
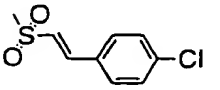
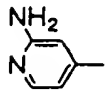
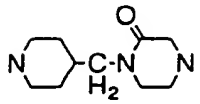
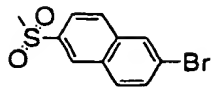
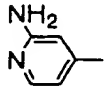
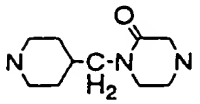
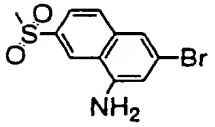
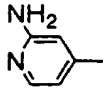
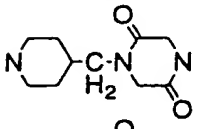
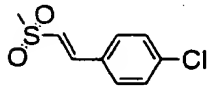
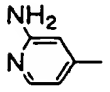
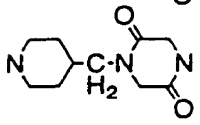
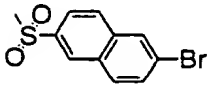
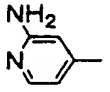
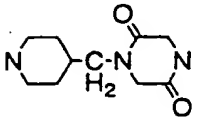
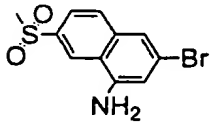
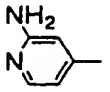
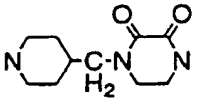
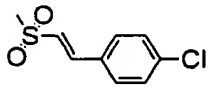
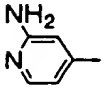
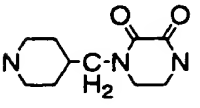
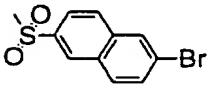
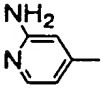
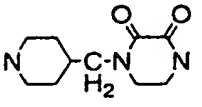
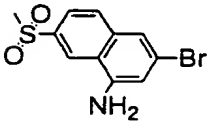
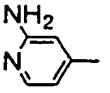
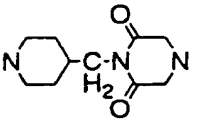
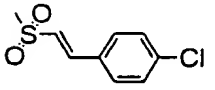
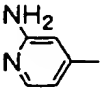
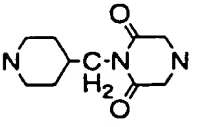
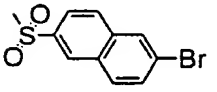
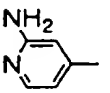
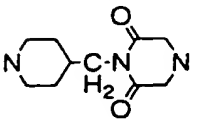
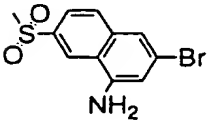
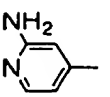
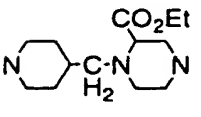
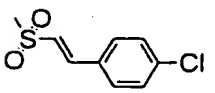
5 9			
6 0			
6 1			
6 2			
6 3			
6 4			
6 5			
6 6			
6 7			
6 8			
6 9			
7 0			

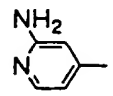
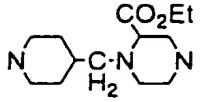
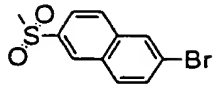
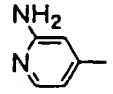
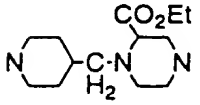
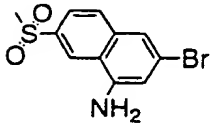
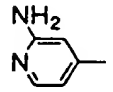
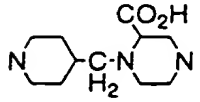
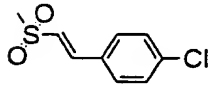
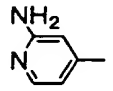
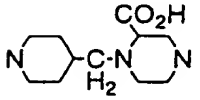
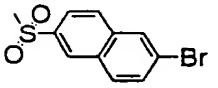
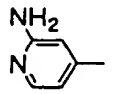
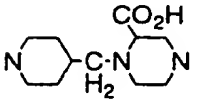
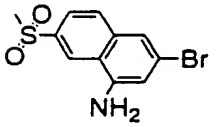
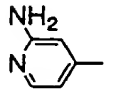
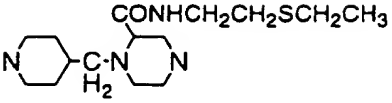
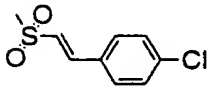
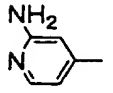
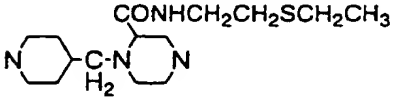
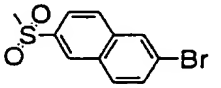
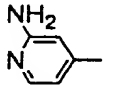
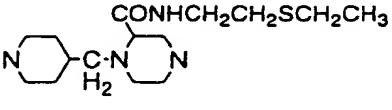
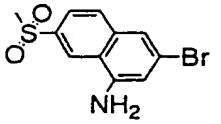
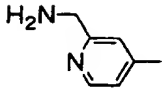
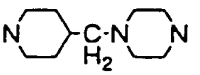
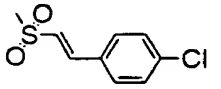
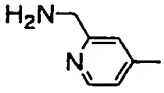
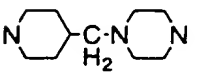
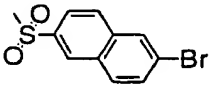
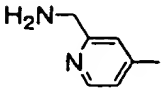
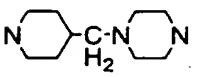
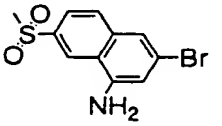
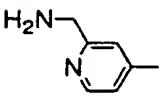
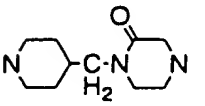
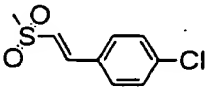
【FIG.7】

	S 1	S 2	S 3
7 1			
7 2			
7 3			
7 4			
7 5			
7 6			
7 7			
7 8			
7 9			
8 0			
8 1			
8 2			

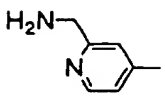
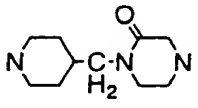
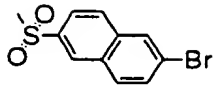
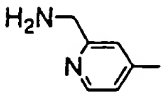
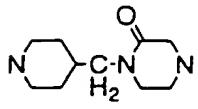
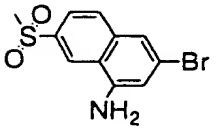
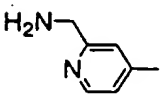
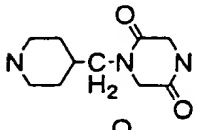
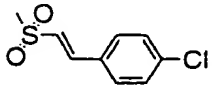
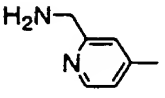
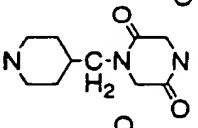
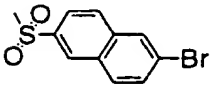
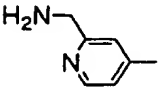
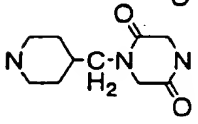
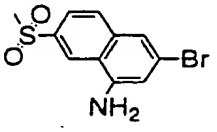
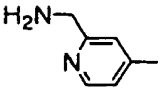
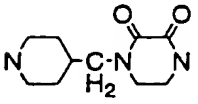
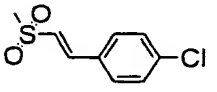
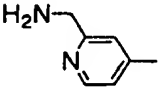
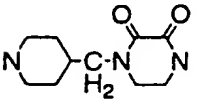
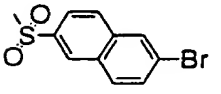
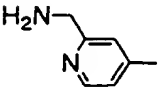
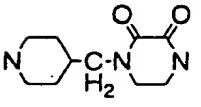
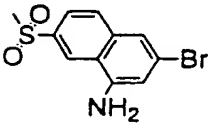
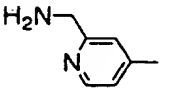
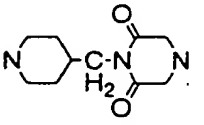
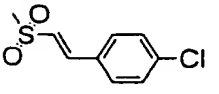
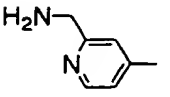
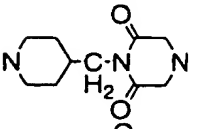
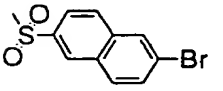
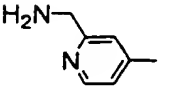
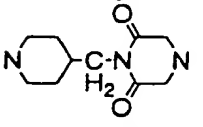
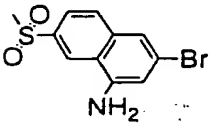
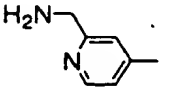
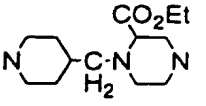
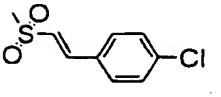
【FIG.8】

	S 1	S 2	S 3
8 3			
8 4			
8 5			
8 6			
8 7			
8 8			
8 9			
9 0			
9 1			
9 2			
9 3			
9 4			

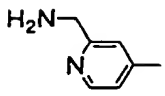
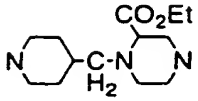
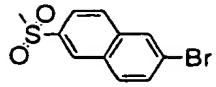
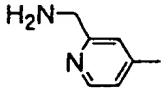
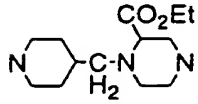
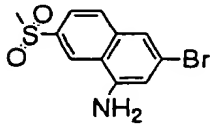
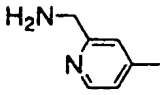
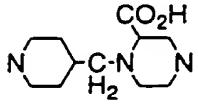
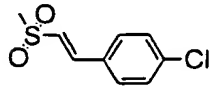
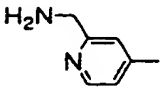
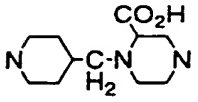
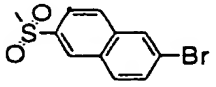
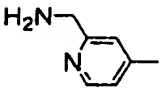
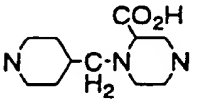
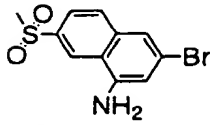
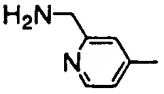
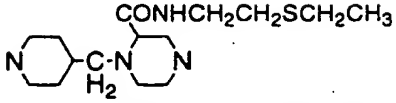
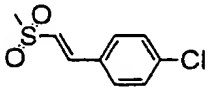
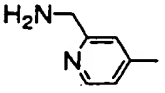
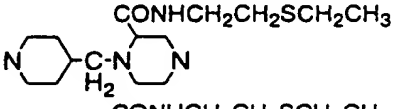
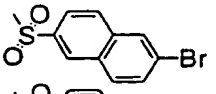
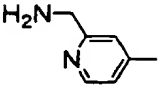
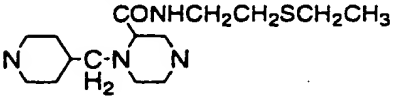
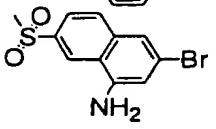
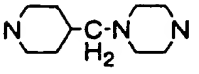
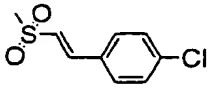
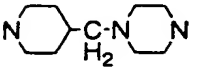
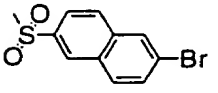
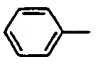
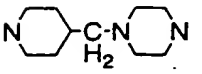
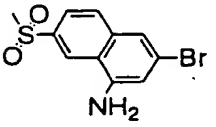
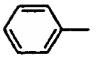
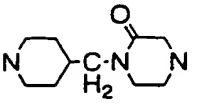
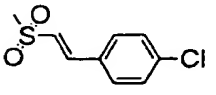
【FIG.9】

	S 1	S 2	S 3
9 5			
9 6			
9 7			
9 8			
9 9			
1 0 0			
1 0 1			
1 0 2			
1 0 3			
1 0 4			
1 0 5			
1 0 6			

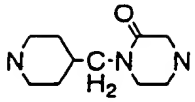
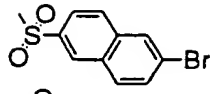
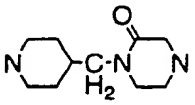
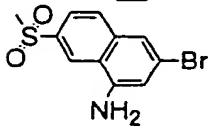
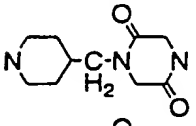
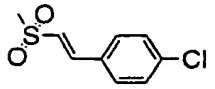
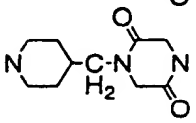
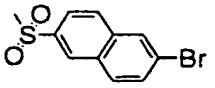
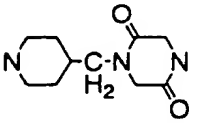
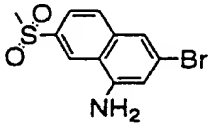
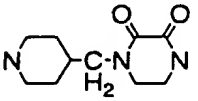
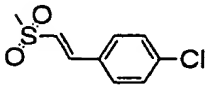
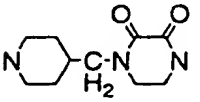
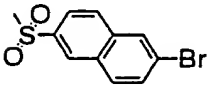
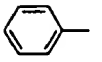
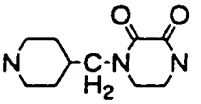
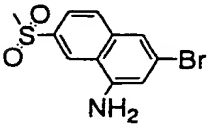
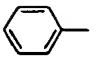
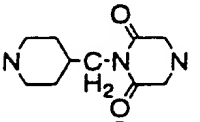
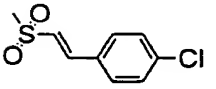
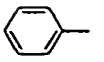
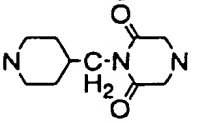
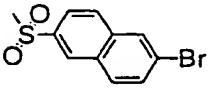
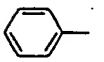
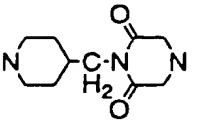
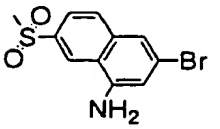
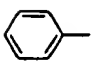
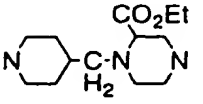
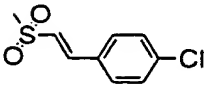
【FIG.10】

	S 1	S 2	S 3
1 0 7			
1 0 8			
1 0 9			
1 1 0			
1 1 1			
1 1 2			
1 1 3			
1 1 4			
1 1 5			
1 1 6			
1 1 7			
1 1 8			

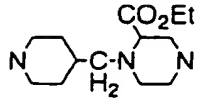
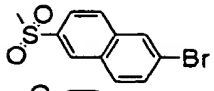
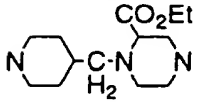
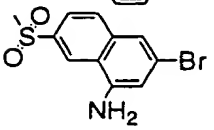
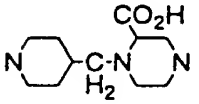
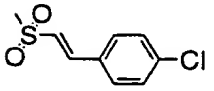
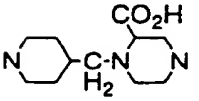
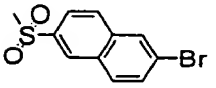
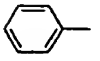
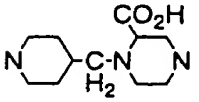
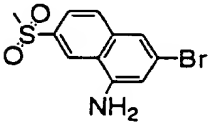
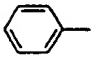
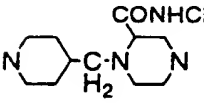
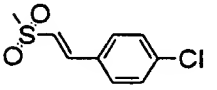
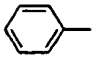
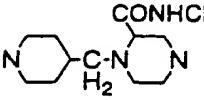
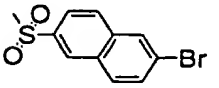
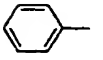
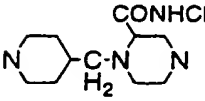
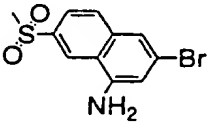
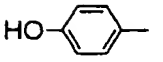
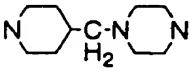
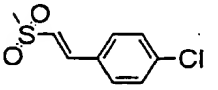
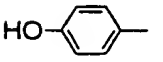
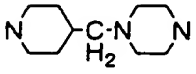
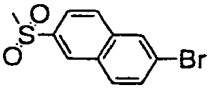
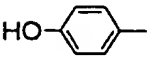
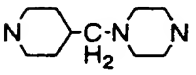
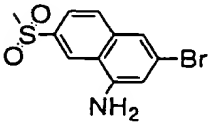
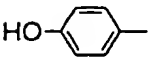
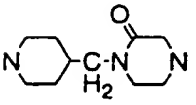
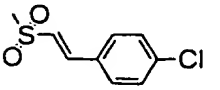
【FIG.11】

	S 1	S 2	S 3
1 1 9			
1 2 0			
1 2 1			
1 2 2			
1 2 3			
1 2 4			
1 2 5			
1 2 6			
1 2 7			
1 2 8			
1 2 9			
1 3 0			

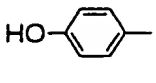
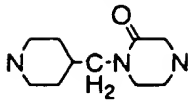
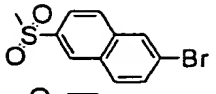
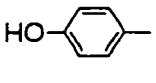
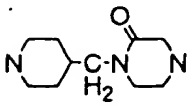
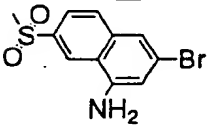
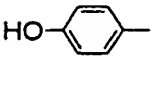
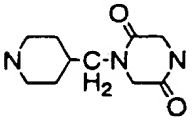
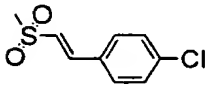
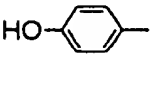
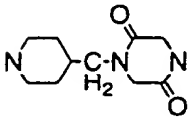
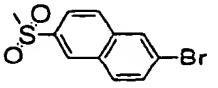
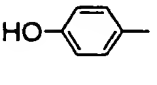
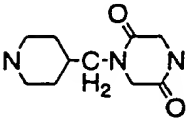
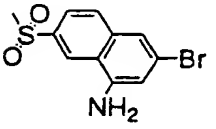
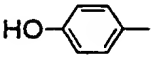
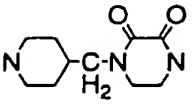
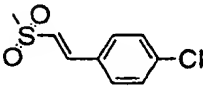
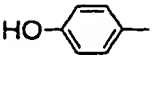
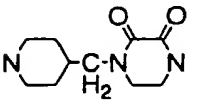
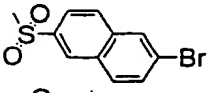
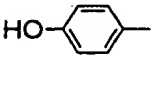
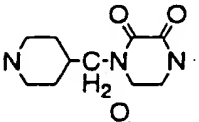
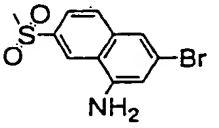
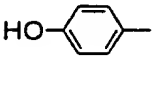
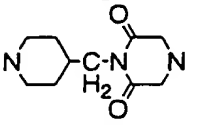
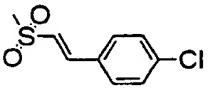
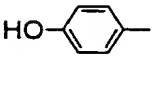
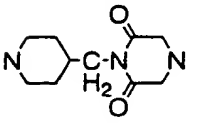
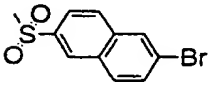
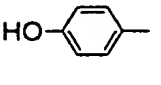
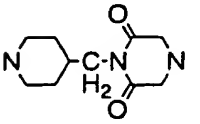
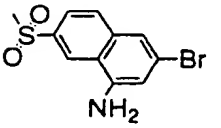
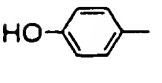
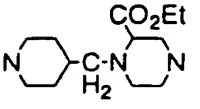
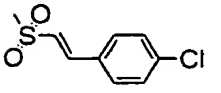
【FIG.12】

	S 1	S 2	S 3
1 3 1			
1 3 2			
1 3 3			
1 3 4			
1 3 5			
1 3 6			
1 3 7			
1 3 8			
1 3 9			
1 4 0			
1 4 1			
1 4 2			

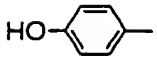
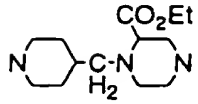
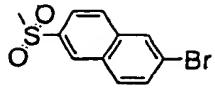
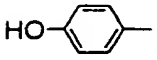
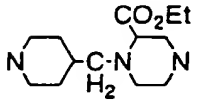
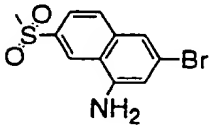
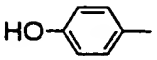
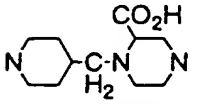
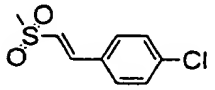
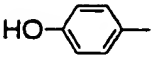
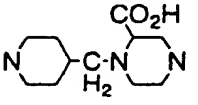
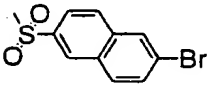
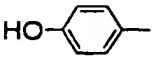
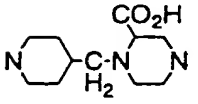
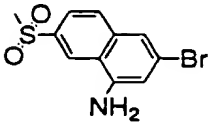
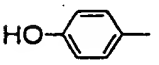
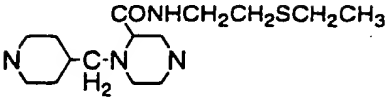
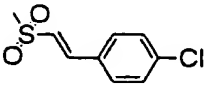
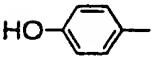
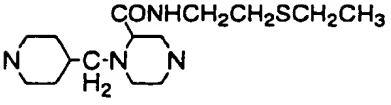
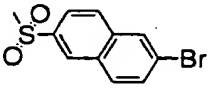
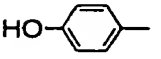
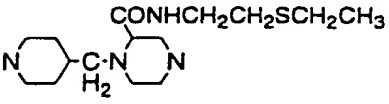
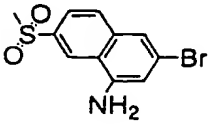
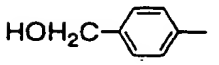
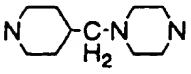
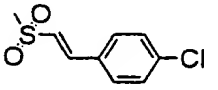
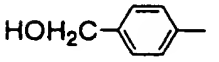
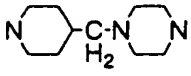
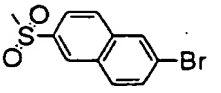
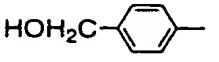
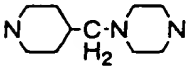
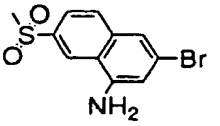
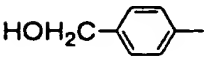
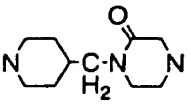
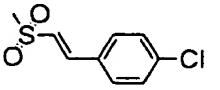
【FIG.13】

	S 1	S 2	S 3
1 4 3			
1 4 4			
1 4 5			
1 4 6			
1 4 7			
1 4 8			
1 4 9			
1 5 0			
1 5 1			
1 5 2			
1 5 3			
1 5 4			

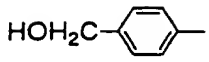
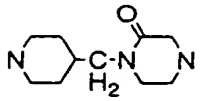
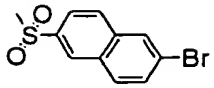
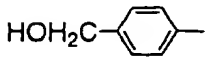
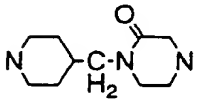
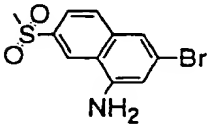
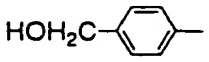
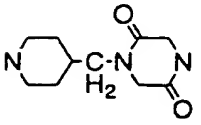
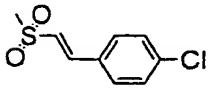
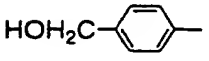
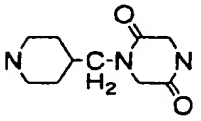
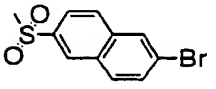
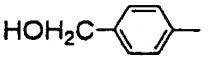
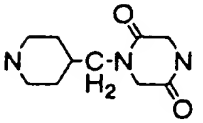
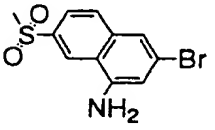
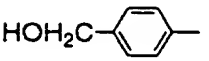
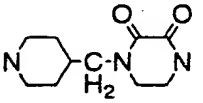
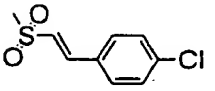
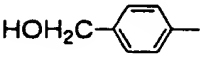
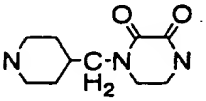
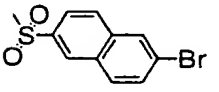
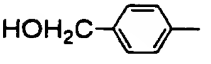
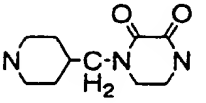
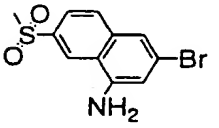
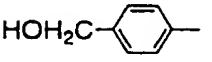
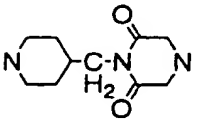
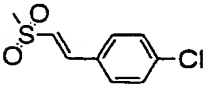
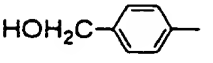
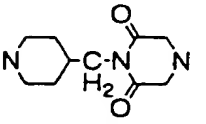
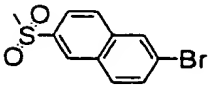
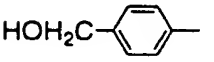
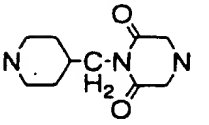
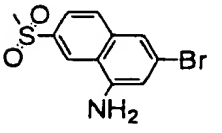
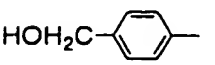
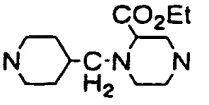
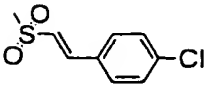
【FIG.14】

	S 1	S 2	S 3
1 5 5			
1 5 6			
1 5 7			
1 5 8			
1 5 9			
1 6 0			
1 6 1			
1 6 2			
1 6 3			
1 6 4			
1 6 5			
1 6 6			

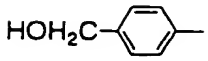
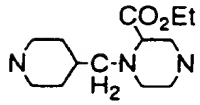
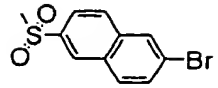
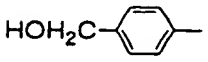
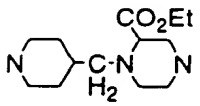
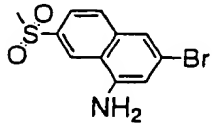
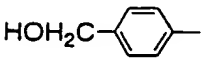
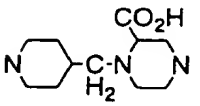
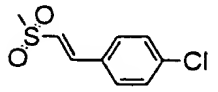
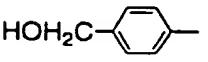
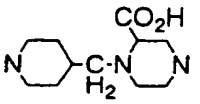
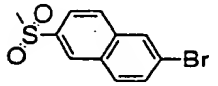
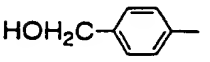
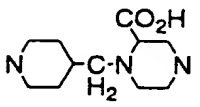
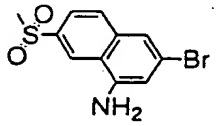
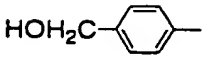
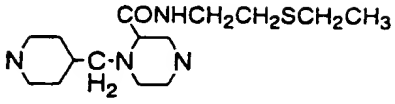
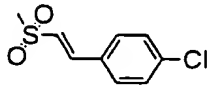
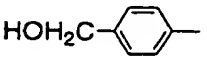
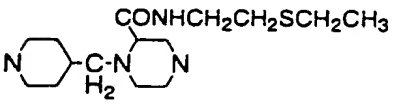
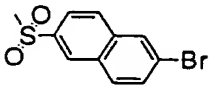
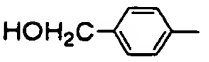
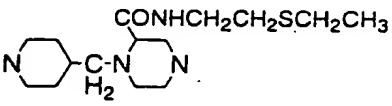
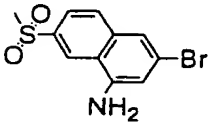
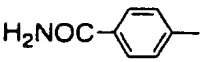
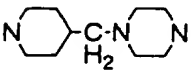
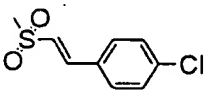
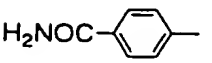
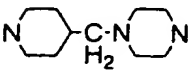
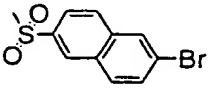
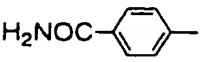
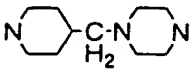
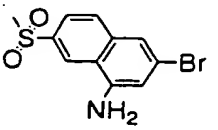
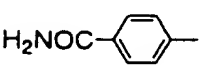
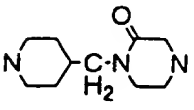
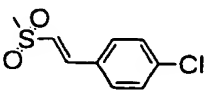
【FIG.15】

	S 1	S 2	S 3
167			
168			
169			
170			
171			
172			
173			
174			
175			
176			
177			
178			

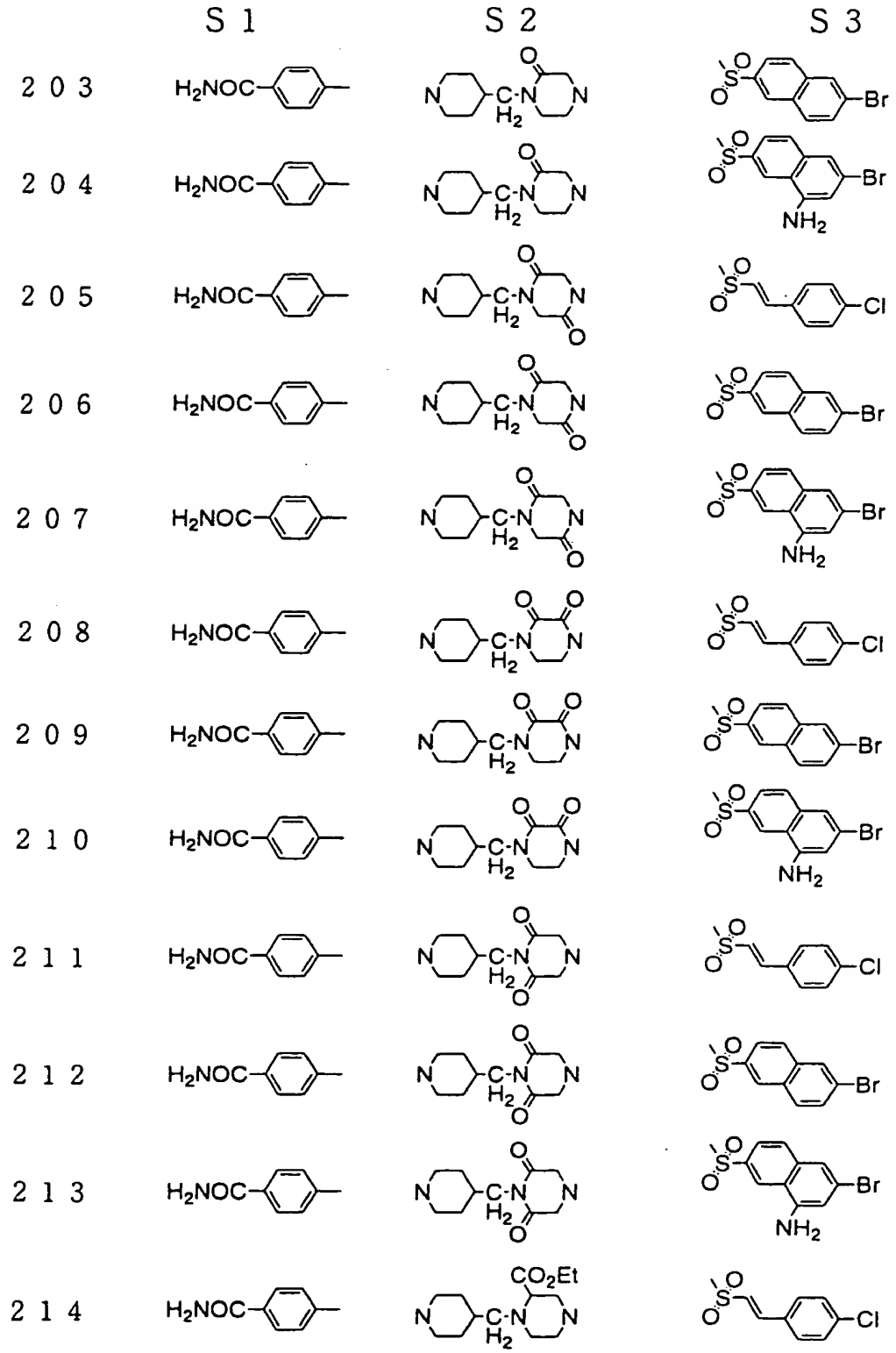
【FIG.16】

	S 1	S 2	S 3
1 7 9			
1 8 0			
1 8 1			
1 8 2			
1 8 3			
1 8 4			
1 8 5			
1 8 6			
1 8 7			
1 8 8			
1 8 9			
1 9 0			

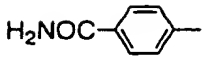
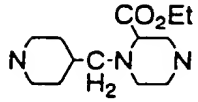
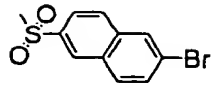
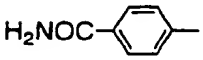
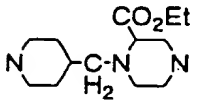
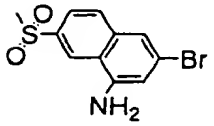
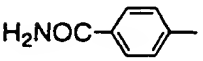
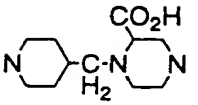
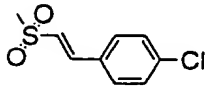
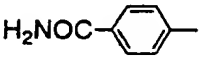
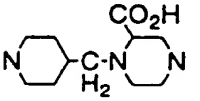
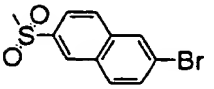
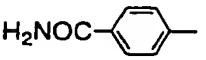
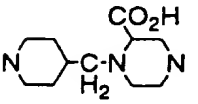
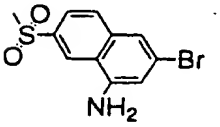
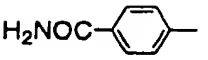
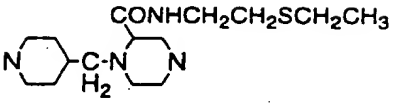
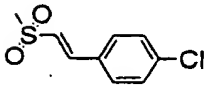
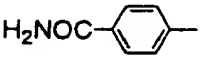
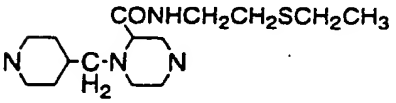
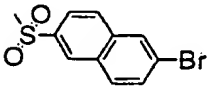
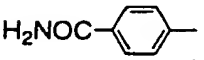
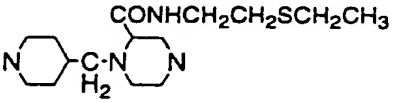
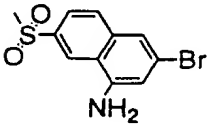
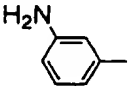
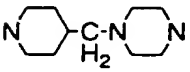
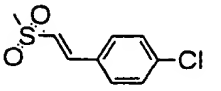
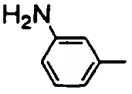
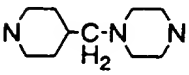
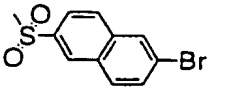
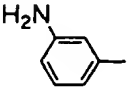
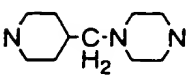
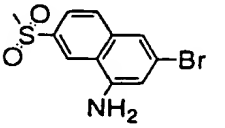
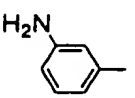
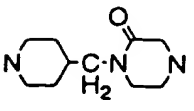
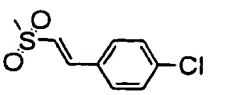
【FIG.17】

	S 1	S 2	S 3
1 9 1			
1 9 2			
1 9 3			
1 9 4			
1 9 5			
1 9 6			
1 9 7			
1 9 8			
1 9 9			
2 0 0			
2 0 1			
2 0 2			

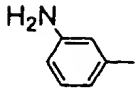
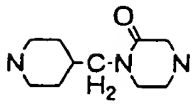
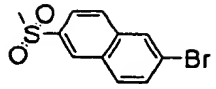
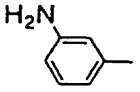
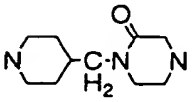
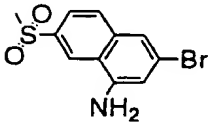
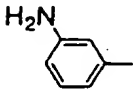
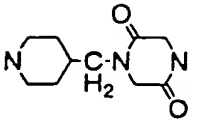
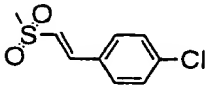
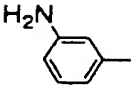
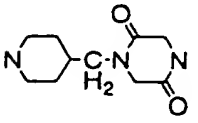
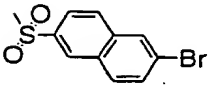
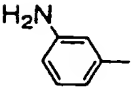
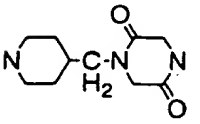
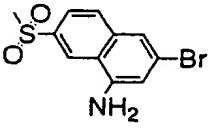
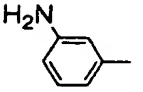
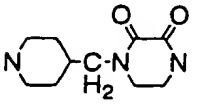
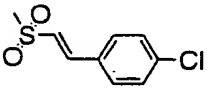
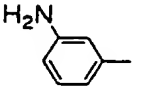
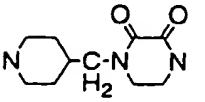
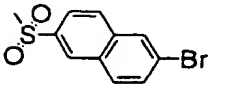
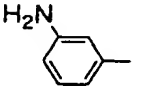
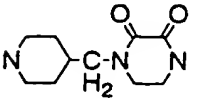
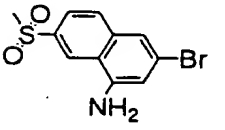
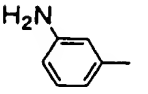
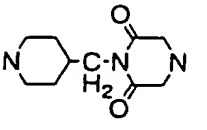
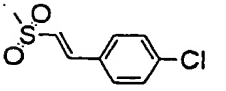
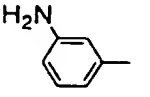
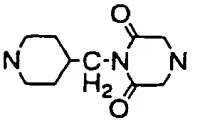
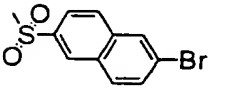
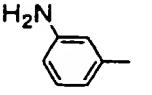
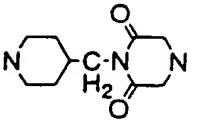
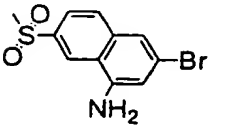
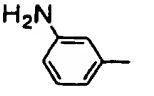
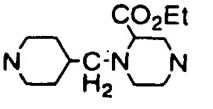
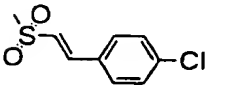
【FIG.18】


S 1
S 2
S 3
2 0 3
2 0 4
2 0 5
2 0 6
2 0 7
2 0 8
2 0 9
2 1 0
2 1 1
2 1 2
2 1 3
2 1 4
H2NOC
Br
NH2
Cl
CO2Et

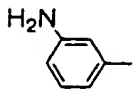
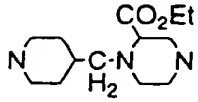
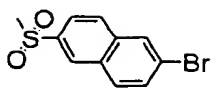
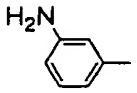
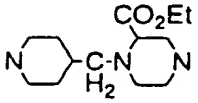
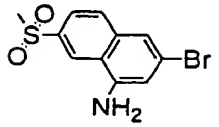
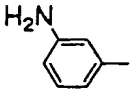
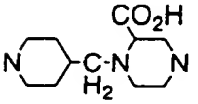
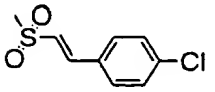
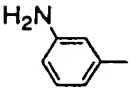
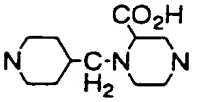
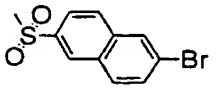
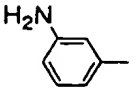
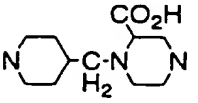
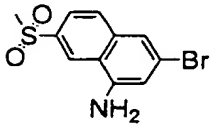
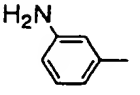
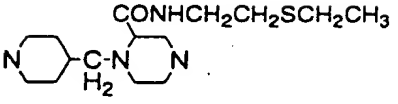
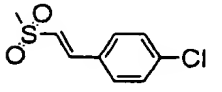
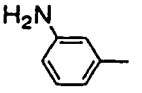
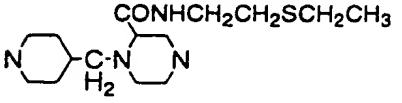
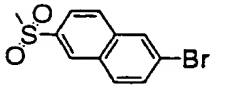
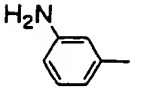
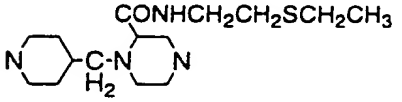
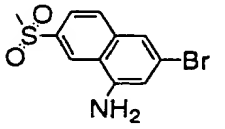
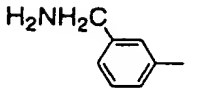
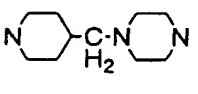
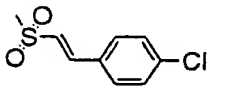
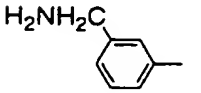
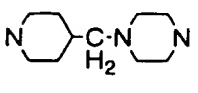
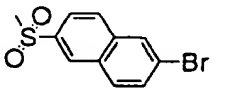
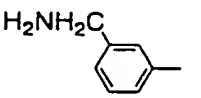
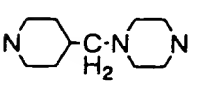
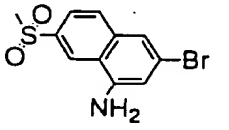
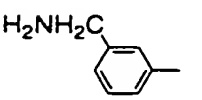
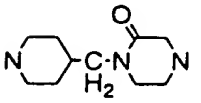
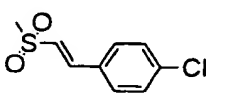
【FIG.19】

	S 1	S 2	S 3
2 1 5			
2 1 6			
2 1 7			
2 1 8			
2 1 9			
2 2 0			
2 2 1			
2 2 2			
2 2 3			
2 2 4			
2 2 5			
2 2 6			

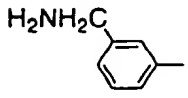
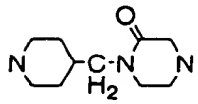
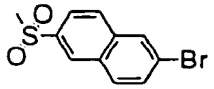
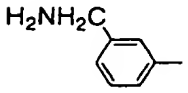
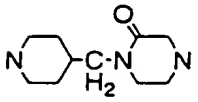
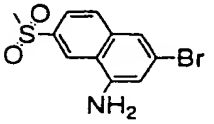
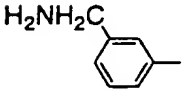
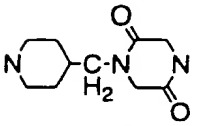
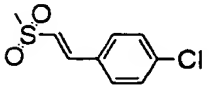
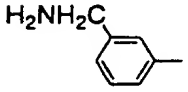
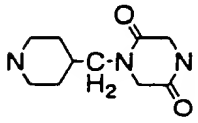
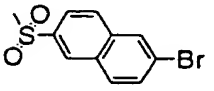
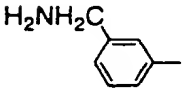
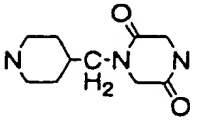
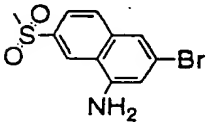
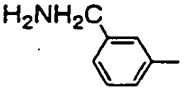
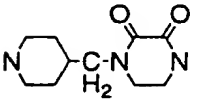
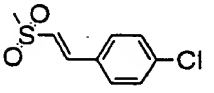
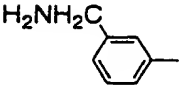
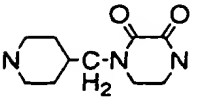
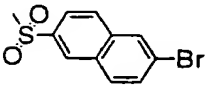
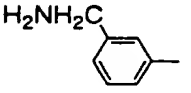
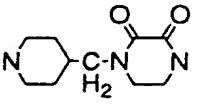
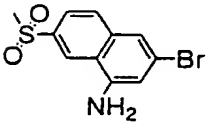
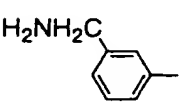
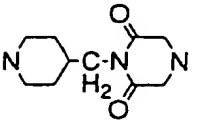
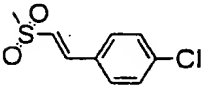
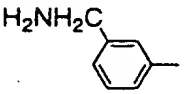
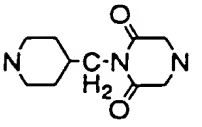
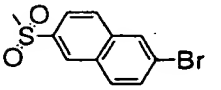
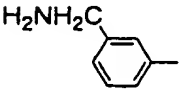
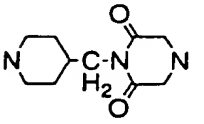
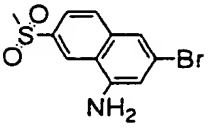
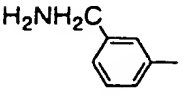
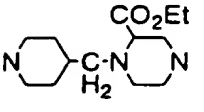
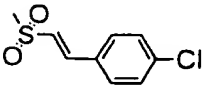
【FIG.20】

	S 1	S 2	S 3
2 2 7			
2 2 8			
2 2 9			
2 3 0			
2 3 1			
2 3 2			
2 3 3			
2 3 4			
2 3 5			
2 3 6			
2 3 7			
2 3 8			

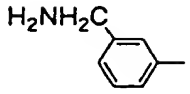
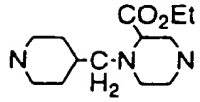
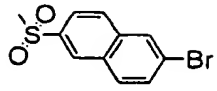
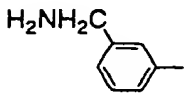
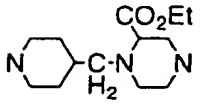
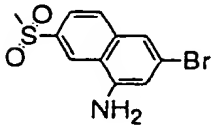
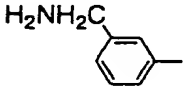
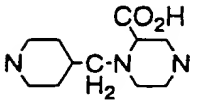
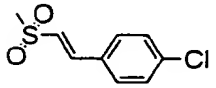
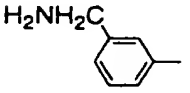
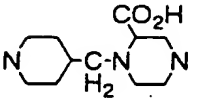
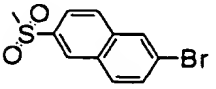
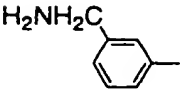
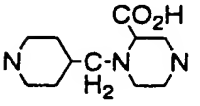
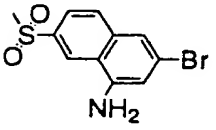
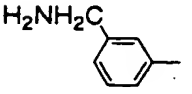
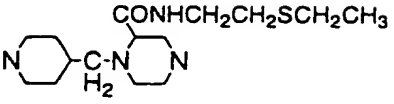
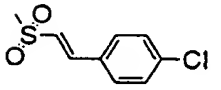
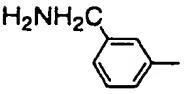
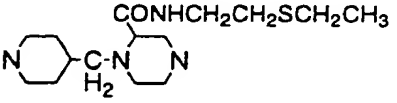
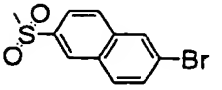
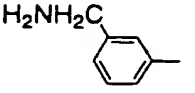
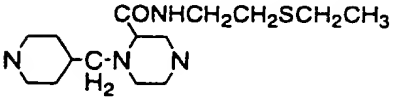
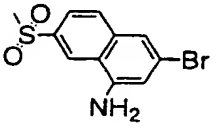
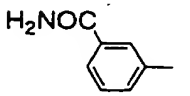
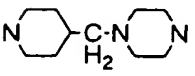
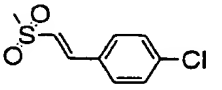
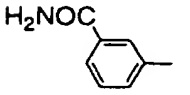
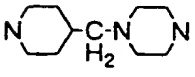
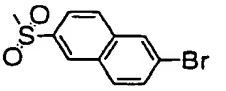
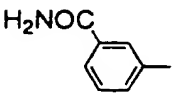
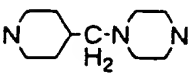
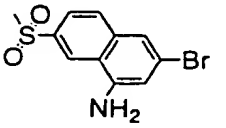
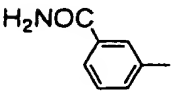
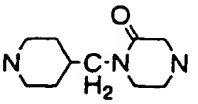
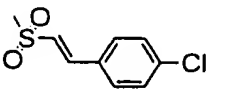
【FIG.21】

	S 1	S 2	S 3
2 3 9			
2 4 0			
2 4 1			
2 4 2			
2 4 3			
2 4 4			
2 4 5			
2 4 6			
2 4 7			
2 4 8			
2 4 9			
2 5 0			

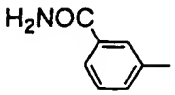
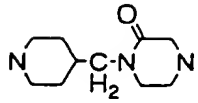
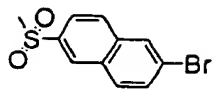
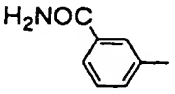
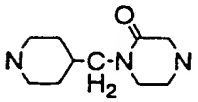
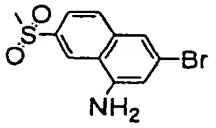
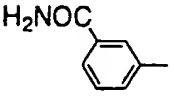
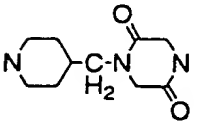
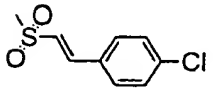
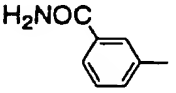
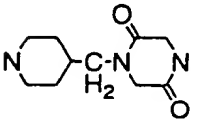
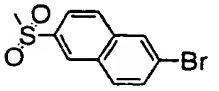
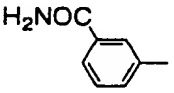
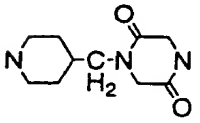
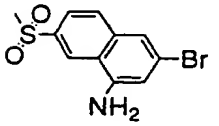
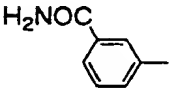
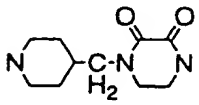
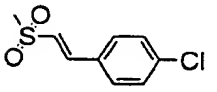
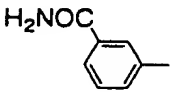
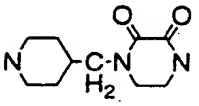
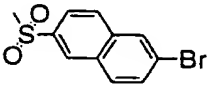
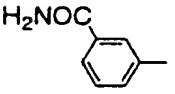
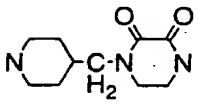
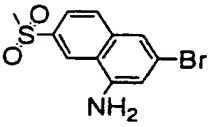
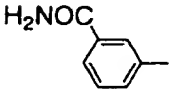
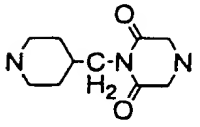
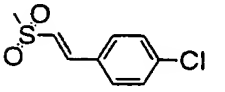
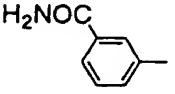
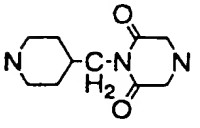
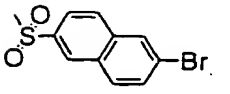
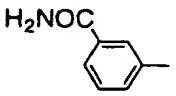
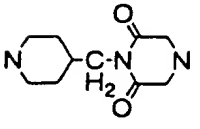
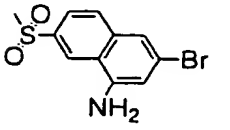
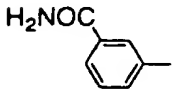
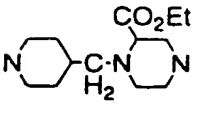
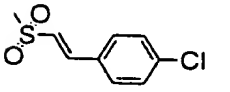
【FIG.22】

	S 1	S 2	S 3
2 5 1			
2 5 2			
2 5 3			
2 5 4			
2 5 5			
2 5 6			
2 5 7			
2 5 8			
2 5 9			
2 6 0			
2 6 1			
2 6 2			

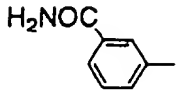
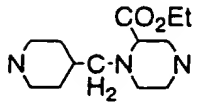
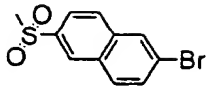
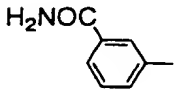
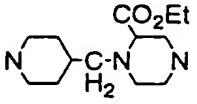
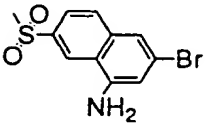
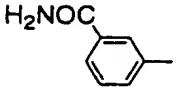
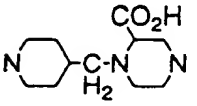
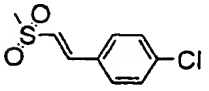
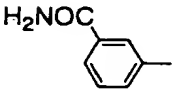
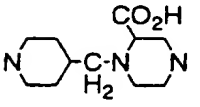
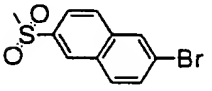
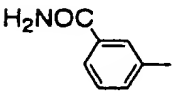
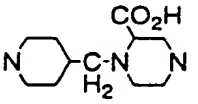
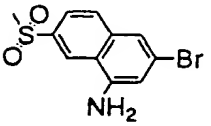
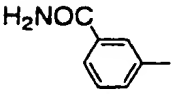
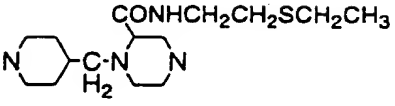
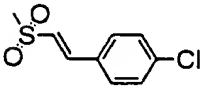
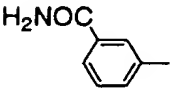
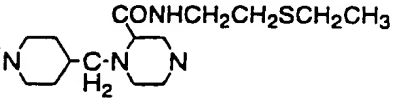
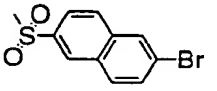
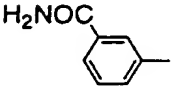
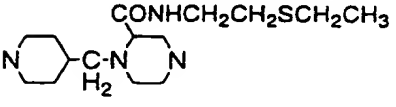
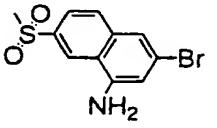
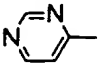
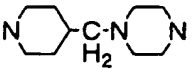
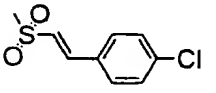
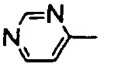
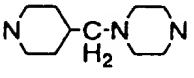
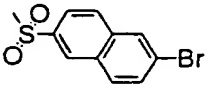
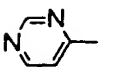
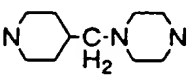
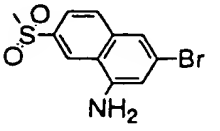
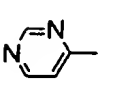
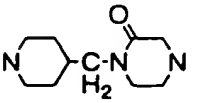
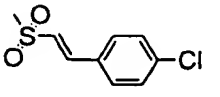
【FIG.23】

	S 1	S 2	S 3
2 6 3			
2 6 4			
2 6 5			
2 6 6			
2 6 7			
2 6 8			
2 6 9			
2 7 0			
2 7 1			
2 7 2			
2 7 3			
2 7 4			

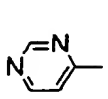
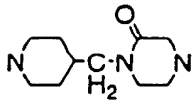
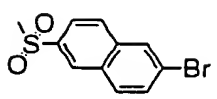
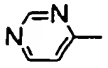
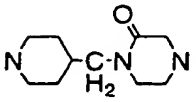
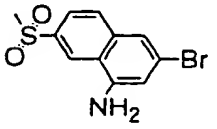
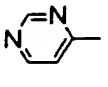
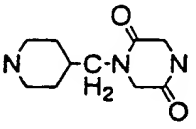
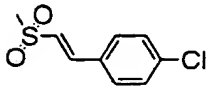
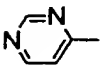
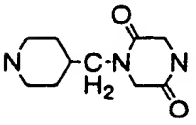
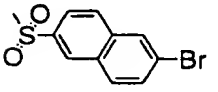
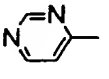
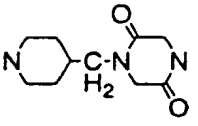
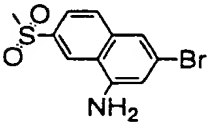
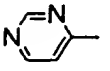
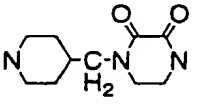
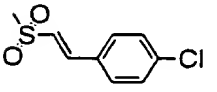
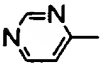
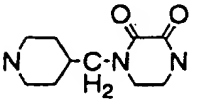
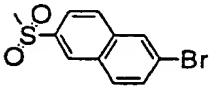
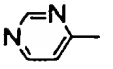
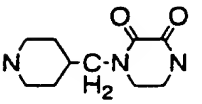
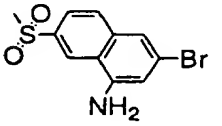
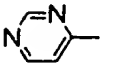
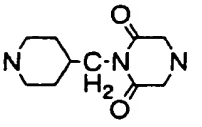
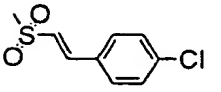
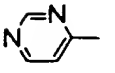
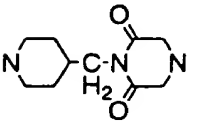
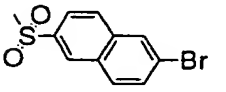
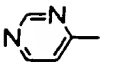
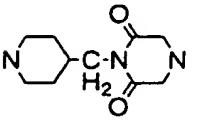
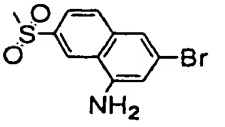
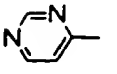
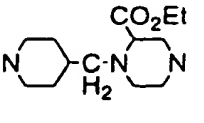
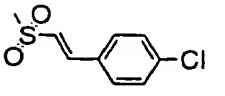
【FIG.24】

	S 1	S 2	S 3
2 7 5			
2 7 6			
2 7 7			
2 7 8			
2 7 9			
2 8 0			
2 8 1			
2 8 2			
2 8 3			
2 8 4			
2 8 5			
2 8 6			

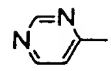
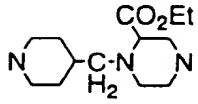
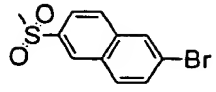
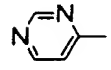
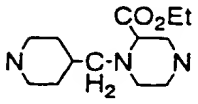
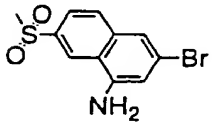
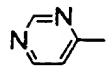
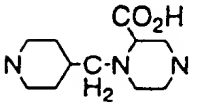
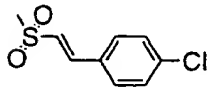
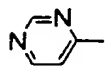
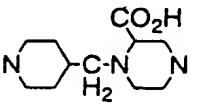
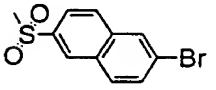
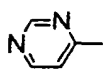
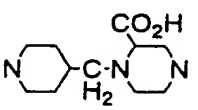
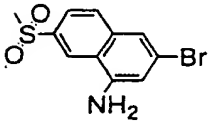
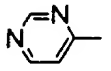
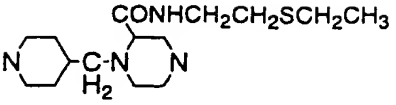
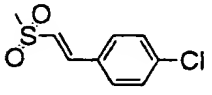
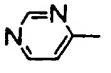
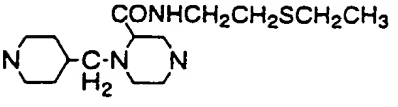
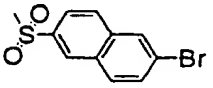
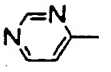
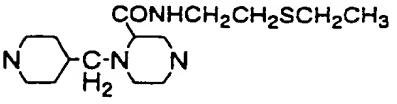
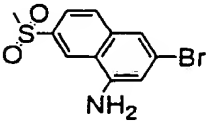
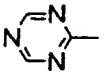
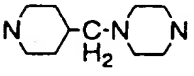
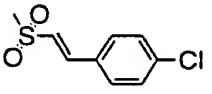
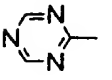
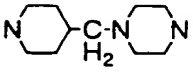
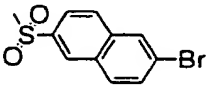
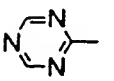
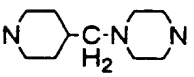
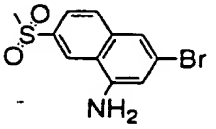
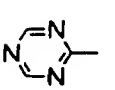
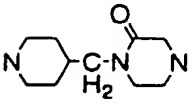
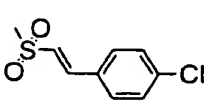
【FIG.25】

	S 1	S 2	S 3
287			
288			
289			
290			
291			
292			
293			
294			
295			
296			
297			
298			

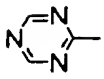
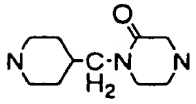
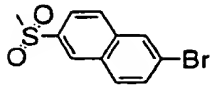
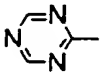
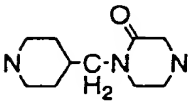
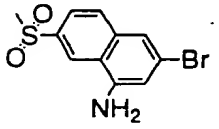
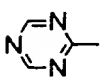
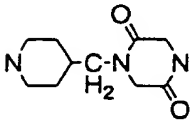
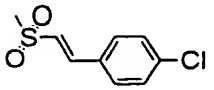
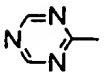
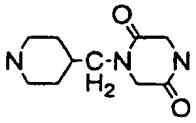
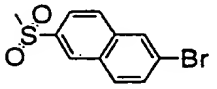
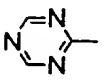
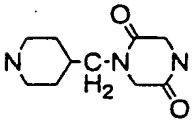
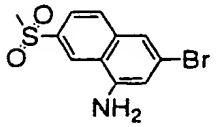
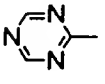
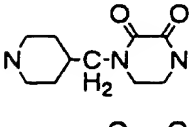
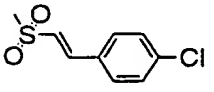
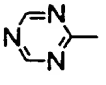
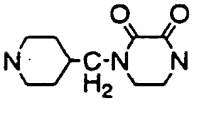
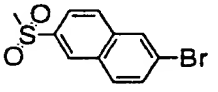
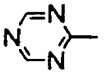
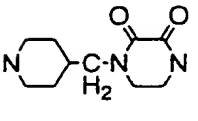
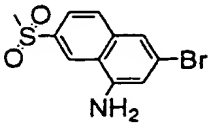
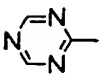
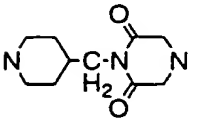
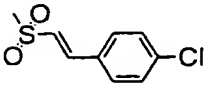
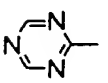
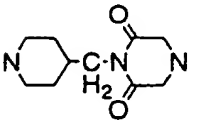
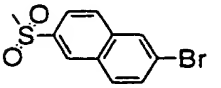
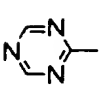
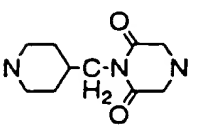
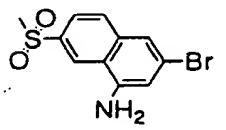
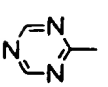
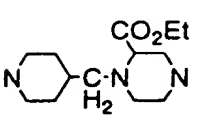
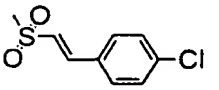
【FIG.26】

	S 1	S 2	S 3
2 9 9			
3 0 0			
3 0 1			
3 0 2			
3 0 3			
3 0 4			
3 0 5			
3 0 6			
3 0 7			
3 0 8			
3 0 9			
3 1 0			

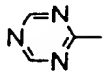
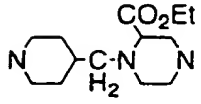
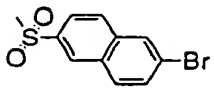
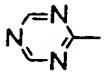
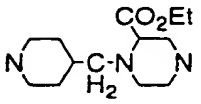
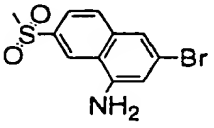
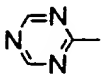
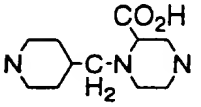
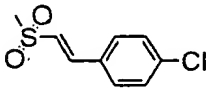
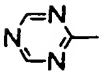
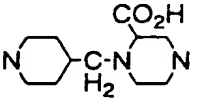
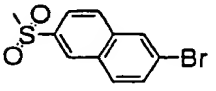
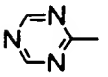
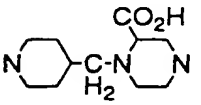
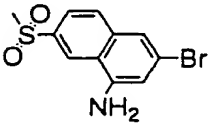
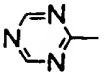
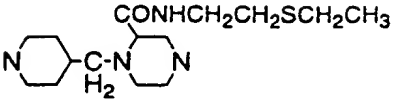
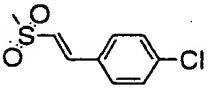
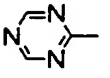
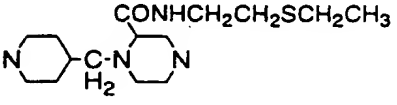
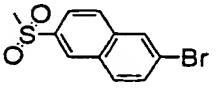
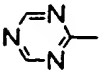
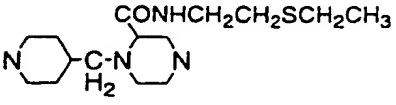
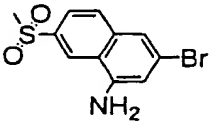
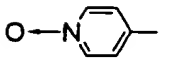
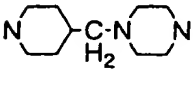
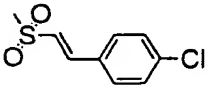
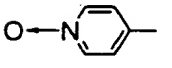
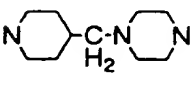
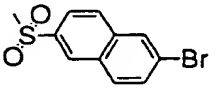
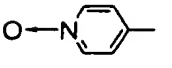
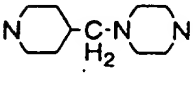
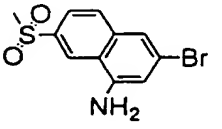
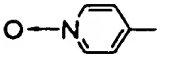
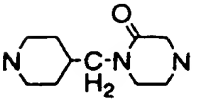
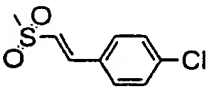
【FIG.27】

	S 1	S 2	S 3
3 1 1			
3 1 2			
3 1 3			
3 1 4			
3 1 5			
3 1 6			
3 1 7			
3 1 8			
3 1 9			
3 2 0			
3 2 1			
3 2 2			

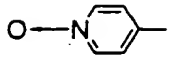
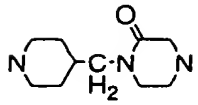
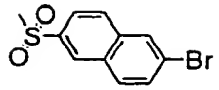
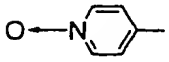
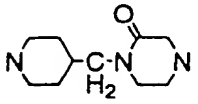
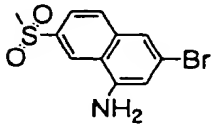
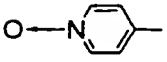
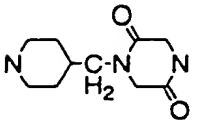
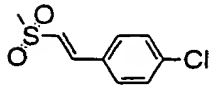
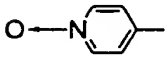
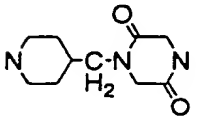
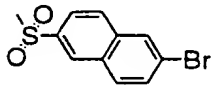
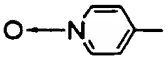
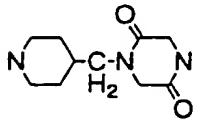
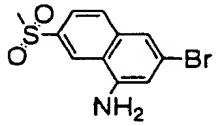
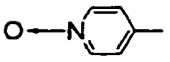
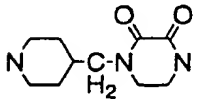
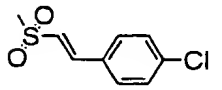
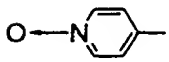
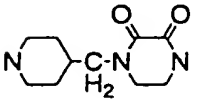
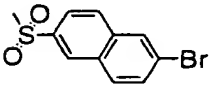
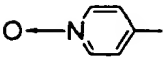
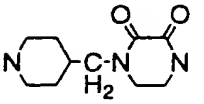
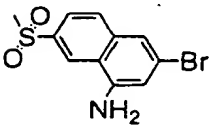
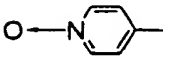
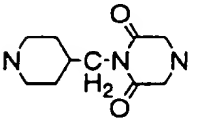
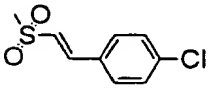
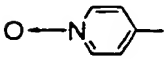
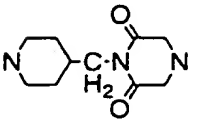
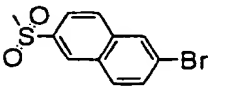
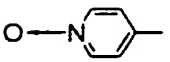
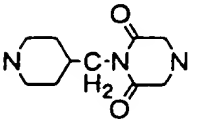
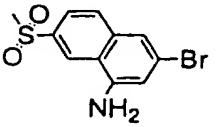
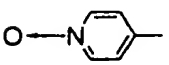
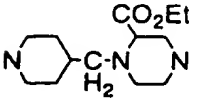
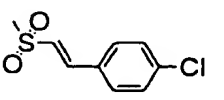
【FIG.28】

	S 1	S 2	S 3
3 2 3			
3 2 4			
3 2 5			
3 2 6			
3 2 7			
3 2 8			
3 2 9			
3 3 0			
3 3 1			
3 3 2			
3 3 3			
3 3 4			

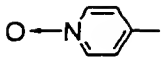
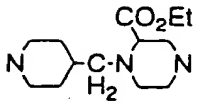
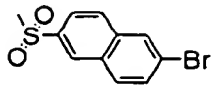
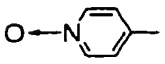
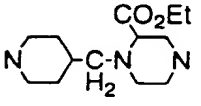
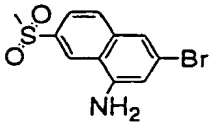
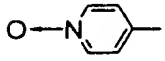
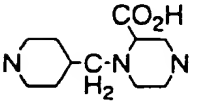
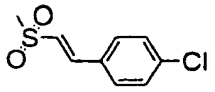
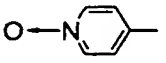
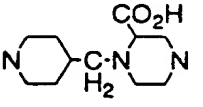
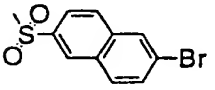
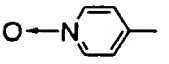
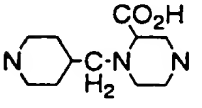
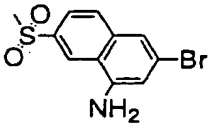
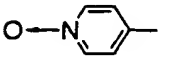
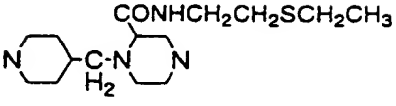
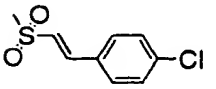
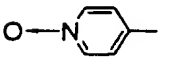
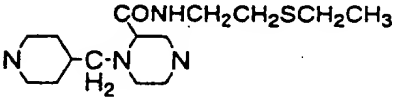
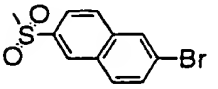
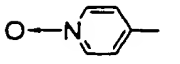
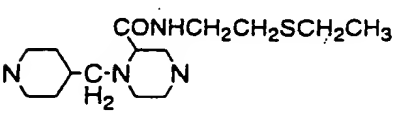
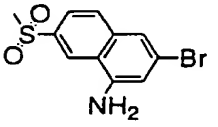
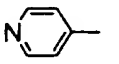
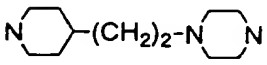
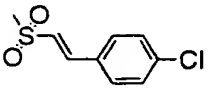
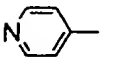
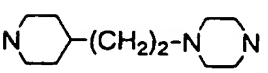
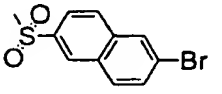
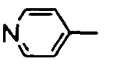
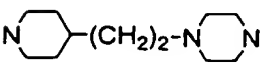
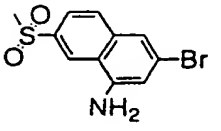
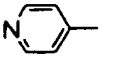
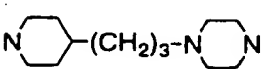
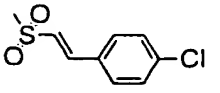
【FIG.29】

	S 1	S 2	S 3
3 3 5			
3 3 6			
3 3 7			
3 3 8			
3 3 9			
3 4 0			
3 4 1			
3 4 2			
3 4 3			
3 4 4			
3 4 5			
3 4 6			

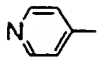
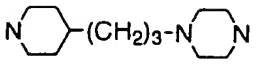
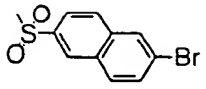
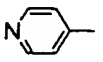
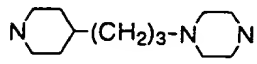
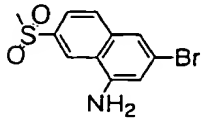
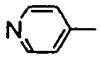
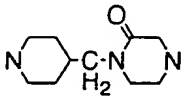
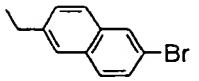
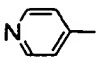
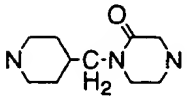
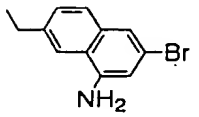
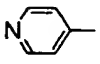
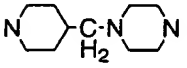
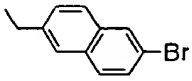
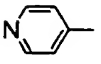
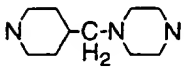
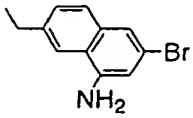
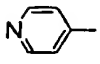
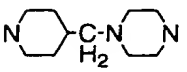
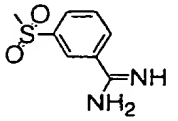
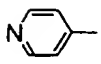
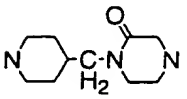
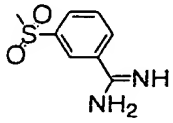
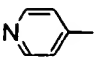
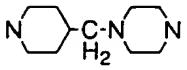
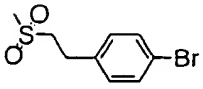
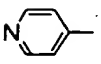
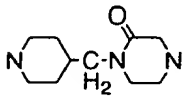
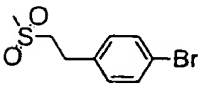
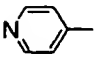
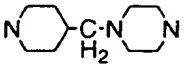
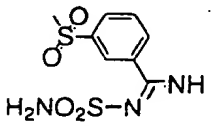
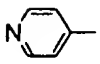
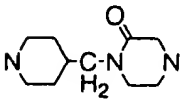
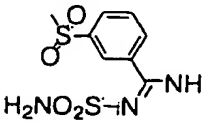
【FIG.30】

	S 1	S 2	S 3
3 4 7			
3 4 8			
3 4 9			
3 5 0			
3 5 1			
3 5 2			
3 5 3			
3 5 4			
3 5 5			
3 5 6			
3 5 7			
3 5 8			

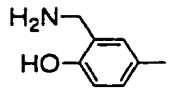
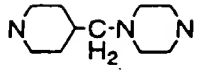
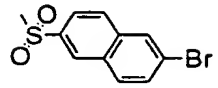
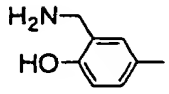
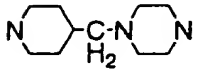
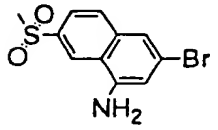
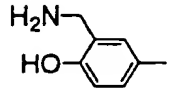
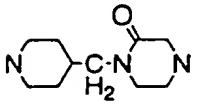
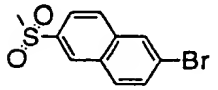
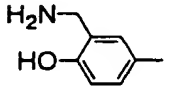
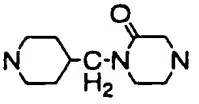
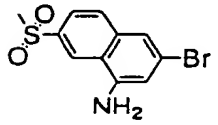
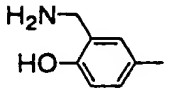
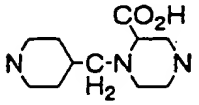
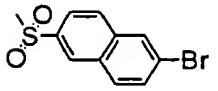
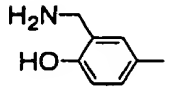
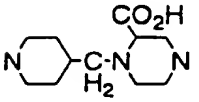
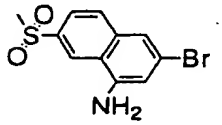
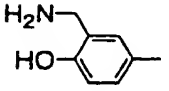
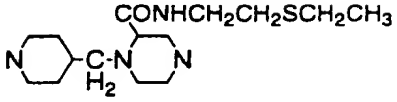
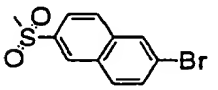
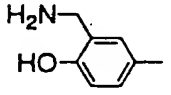
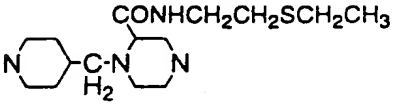
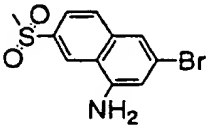
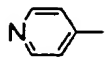
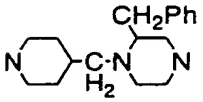
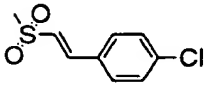
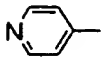
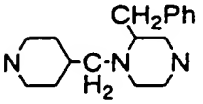
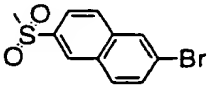
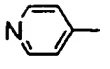
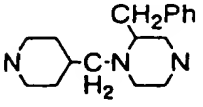
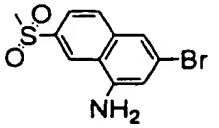
【FIG.31】

	S 1	S 2	S 3
3 5 9			
3 6 0			
3 6 1			
3 6 2			
3 6 3			
3 6 4			
3 6 5			
3 6 6			
3 6 7			
3 6 8			
3 6 9			
3 7 0			

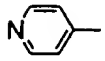
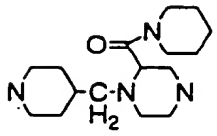
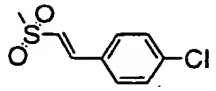
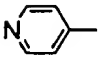
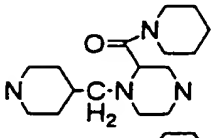
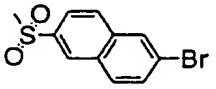
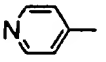
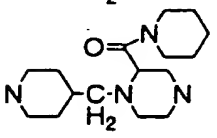
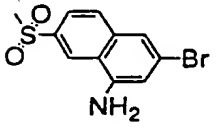
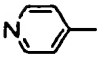
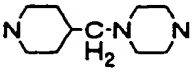
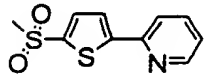
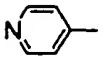
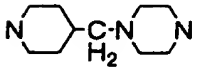
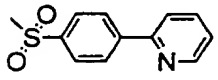
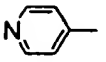
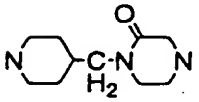
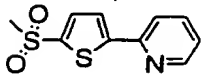
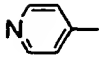
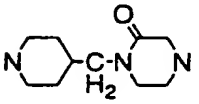
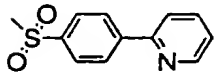
【FIG.32】

	S 1	S 2	S 3
3 7 1			
3 7 2			
3 7 3			
3 7 4			
3 7 5			
3 7 6			
3 7 7			
3 7 8			
3 7 9			
3 8 0			
3 8 1			
3 8 2			

【FIG.33】

	S 1	S 2	S 3
3 8 3			
3 8 4			
3 8 5			
3 8 6			
3 8 7			
3 8 8			
3 8 9			
3 9 0			
3 9 1			
3 9 2			
3 9 3			

【FIG.34】

	S 1	S 2	S 3
3 9 4			
3 9 5			
3 9 6			
3 9 7			
3 9 8			
3 9 9			
4 0 0			

4 0 1 Methanesulfonate of the compound in Example No.3

4 0 2 Methanesulfonate of the compound in Example No.23

[TYPE OF THE DOCUMENT] Abstract

[ABSTRACT]

[Subject] Novel compounds which have a potent and specific inhibitory action of activated blood coagulation factor X (FXa), are orally administrable for prevention and/or therapy of disease caused by thrombus or embolus, have less side effects such as bleeding tendency, and clinically convenient; processes for producing thereof; and pharmaceutical compositions containing at least one compound thereof as an active ingredient are provided.

[Means for Solution] The subjects described above are solved by novel aromatic compounds having cyclic amino groups.

[Selected Drawing] None